The New England
Journal of Medicine

Copyright, 1956, by the Massachusetts Medical Society

Volume 255 JULY 26, 1956 Number 4

PLASMA PEPSINOGEN IN PEPTIC-ULCER DISEASE AND OTHER GASTRIC DISORDERS*

A Clinical and Laboratory Evaluation

CARL S. HOAR, JR., M.D.,† AND J. R. BROWNING, M.D.‡

With the Technical Assistance of Robert G. Simpson

BOSTON

PEPSIN consists of a protein molecule that may be crystallized out of a solution of crystallin pepsinogen after incubation at pH 4.65. It is a powerful proteolytic enzyme implicated as a causative agent in peptic-ulcer disease, in which it is often associated with an elevated gastric acidity. However, its relation to the chloride ion in gastric juice is not a linear one, and occasionally in ulcer disease the pepsin will be normal or low in the gastric juice when the acidity is high and vice versa. This does not seem remarkable when one considers the various modes of stimulation of gastric secretion. Gastrin, for instance, the chemical mediator, only stimulates the production of hydrochloric acid. Vagal stimulus, however, will increase the output of both pepsin and acid as well as mucin. It seems reasonable that the frequent association of elevated gastric pepsin and peptic-ulcer disease has some etiologic significance.

There has been considerable literature in the past ten years regarding a proteolytic enzyme in the urine called uropepsin that disappears after total gastrectomy, is low or absent in pernicious anemia, tends to be elevated in duodenal ulcer and falls after partial gastrectomy.[1-5] This enzyme has been thought to have the same precursor as gastric pepsin, — namely, pepsinogen, — excreted through the kidneys from the plasma. It has a proportionate increase with the intravenous administration of pepsinogen.[4] The laboratory determination of this substance involves the collection of a twenty-four-hour specimen of urine and a colorimetric test in urine, which has many interfering chromogenic substances.

In 1952 Mirsky et al.[6,7] described a simple test for measuring the level of a proteolytic enzyme in plasma or serum that they termed pepsinogen.[8] They described the presence of three proteolytic enzymes with the following distinctive characteristics: cathepsin, an enzyme with maximum proteolytic effect at pH 4.5; an enzyme with maximum proteolytic effect at pH 1.5 that is not inactivated by alkalinization; and an enzyme that optimally is activated by adjustment of the pH to 1.5 but destroyed by subsequent adjustment of pH to 10. It is the last enzyme that is apparently related to gastric secretory function and is designated as pepsinogen.

The work of Mirsky and his associates indicated that the laboratory analysis of plasma pepsinogen was quite reproducible and that the individual value was fairly constant from day to day, had little variation in relation to time of day, and was increased in hypersecretory states such as peptic-ulcer disease and decreased in hyposecretory states such as those after subtotal gastrectomy or pernicious anemia.

The simplicity of the procedure, its reproducibility and the absence of the obvious sources of error that are apt to be inherent in quantitative urinary studies, particularly when colorimetric methods are used, made us consider it worthy of further study.

METHOD (MIRSKY'S MODIFICATION OF ANSEN'S METHOD)

Reagents

Reagents are as follows:

Hemoglobin substrate, 2.5 per cent (Difco) adjusted to pH 1.5.
1.5-normal hydrochloric acid.
0.3-normal hydrochloric acid.
0.3-normal trichloracetic acid.
0.5-normal sodium hydroxide.
Folin–Ciocalteau phenol reagent.

*From the Veterans Administration Hospital, West Roxbury, Massachusetts, and the Surgical Research Laboratory of the Department of Surgery, Peter Bent Brigham Hospital and Harvard Medical School.

†Instructor in surgery, Harvard Medical School; junior associate in surgery, Peter Bent Brigham Hospital; associate chief of surgery, Veterans Administration Hospital.

‡Assistant in medicine, Harvard Medical School; assistant in medicine, Peter Bent Brigham Hospital; assistant chief of medicine, Veterans Administration Hospital.

Procedure

In a 15-ml. centrifuge tube 2 ml. of oxalated plasma is added to 10 ml. of 2.5 per cent hemoglobin substrate. One should be careful in drawing the blood to prevent hemolysis. The plasma should be frozen immediately if storage is necessary. The mixture is adjusted to pH 1.5 by the addition of 0.3 ml. of 1.5-normal hydrochloric acid and then brought to a volume of 15 ml. with water. An aliquot of 6 ml. of the mixture is incubated at 37°C. for twenty-four

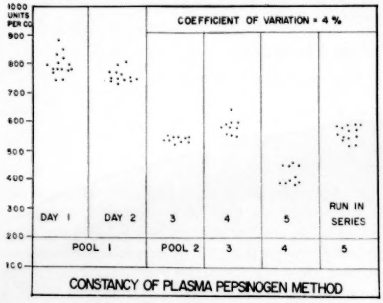


FIGURE 1. *Multiple Determinations on Pooled Plasma to Evaluate Laboratory Error.*

hours. The reaction is stopped by the addition of 10 ml. of 0.3-normal trichloracetic acid. The mixture is filtered with the use of Whatman No. 3 paper. The concentration of chromogenic substance originally present in the mixture is determined by an analysis of a filtrate prepared from the second 6-ml. aliquot added to 10 ml. of trichloracetic acid; 2 ml. of filtrate from each of these is put into spectrophotometer tubes to which 3 ml. of trichloracetic acid and 10 ml. of 0.5-normal sodium hydroxide and 3 ml. of dilute phenol reagent (one part reagent and two parts water) are added. Color is developed immediately, and the tubes are read five minutes after the phenol is added. The wave length used is 420 millimicrons on a Coleman spectrophotometer, model No. 14. The percentage transmission is read and converted to optical density. For the calculations the optical density of the incubated sample minus the optical density of the unincubated sample times ten equals the micrograms of tyrosinelike substance released in 1 ml. of plasma.

This method was tested for reproducibility in the following manner. Five pools of plasma were obtained from the clinical laboratory, selection being made at random. Ten determinations from three pools were run simultaneously on three different days. One pool was divided in half, and 15 determinations run on two different days. A further pool was divided into 7 aliquots, and 2 determinations run on each on seven different days, during which all reagents used in the procedure were changed three times. The results, which checked quite closely, are presented graphically in Figure 1. The average coefficient of variation inherent in the procedure was calculated to be 4 per cent. Throughout the study, frozen stored-plasma specimens were retested, and the results checked against those from the same sample up to one year previously. The reproducibility was always good. Forty-five patients, selected at random, had an average value of plasma pepsinogen of 603.5 tyrosine units originally. Twelve to eighteen months later, the plasma having been stored in a frozen state during this time, the average value was 540.7 tyrosine units. This is just outside the expected laboratory error inherent in the method. Values obtained from serum and plasma were compared, and no significant difference noted.

To check the constancy from day to day determinations were made daily for nine to thirteen days on 5 normal persons. The coefficient of variation averaged 11.7 per cent, with a range of 4.7 to 21.5 per cent. In the work of Mirsky et al.[7] this figure was 15 per cent.

To determine variations throughout the same day hourly specimens were obtained from 4 subjects over a nine-hour period beginning in a fasting state and with two average meals eaten in the study period. The average coefficient of variation was 10 per cent, the range in the 4 being 12.6 to 7.6 per cent. The variations seemed to be completely unrelated to meals. The figure given by Mirsky et al. for coefficient of variation in hourly determinations corresponding to these was 8 per cent. They also used a variety of foods and found no significant fluctuation. The results indicate a certain constancy in level regardless of time of day.

Results

Clinical Studies

Preliminary studies evaluating the plasma pepsinogen test as a clinical tool were begun in February, 1954. A control group of asymptomatic hospital personnel and patients who either had no clinical evidence of peptic-ulcer disease or had negative gastrointestinal x-ray examinations were studied. This group consisted of 89 persons. The mean value obtained in this group was 486 tyrosine units, with a standard deviation of 163 tyrosine units.

A group of 74 patients with radiologically demonstrated duodenal ulcers were studied at the same time. The mean value in this group was 689 tyrosine units, with a standard deviation of 197 tyrosine units.

A third group of 47 patients who had had radical subtotal gastrectomy (85 per cent) for duodenal ulcers had a mean level of 314 tyrosine units, with a standard deviation of 93 tyrosine units.

These three sets of figures are statistically significant when compared with one another ($P<0.01$).

These results are presented in the form of frequency-distribution curves (Fig. 2) and also in Table 1.

Fifteen patients with benign gastric ulcer were studied. Seven of these had resections and histologic proof of benignancy, and the other 8 had all the clinical and radiologic characteristics of benign gastric ulcer, including prompt healing on a medical regimen without apparent recurrence. The mean value in this group was 705 tyrosine units, with a standard deviation of 298 tyrosine units (Table 1). There was no significant difference between this group and the duodenal-ulcer group, but when it was compared with the control group (despite the high standard deviation) the probability that the difference was due to chance was less than 1:100 ($P<0.01$). However, no attempt was made to separate antral ulcers from those elsewhere in the stomach as in the study of Hirschowitz.[3]

It is interesting in this regard to cite the case of one thirty-year-old man with ulcer symptoms and weight loss of many months' duration. He was found to have a prepyloric ulcer in the lesser curvature with signs suggestive of cancer on the first gastrointestinal series, but not on the second. Gastroscopy was reported to show a benign ulcer in the position noted on x-ray examination. Gastric analysis revealed no free hydrochloric acid after histamine. The plasma pepsinogen was 1660 tyrosine units, a very high value. This

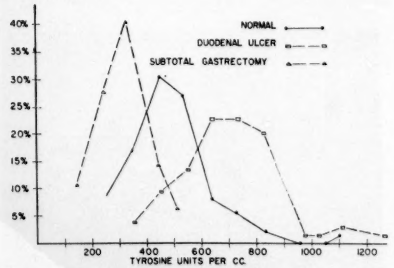


FIGURE 2. *Frequency-Distribution Curves, Illustrating Plasma Pepsinogen Results in Normal, Duodenal-Ulcer and Subtotal-Gastrectomy Patients.*

suggested strongly that this ulcer was benign, and influenced the decision to give conservative treatment. The ulcer healed radiologically, and he has been asymptomatic for three months. He will be followed closely.

The diagnosis of carcinoma of the stomach was proved histologically in 5 cases in which studies were carried out. The mean value was 388 tyrosine units, with a standard deviation of 36. This mean is significantly lower than that of the control and gastric-ulcer groups. A low plasma pepsinogen in the face of gastric ulceration seems to be a strong indication of cancer. Many more cases must be studied before any conclusions may be reached.*

Five patients with total or nearly total gastrectomies were studied. In these cases a mean of 147 tyrosine units, with a standard deviation of 77, was obtained.

Many of the patients with simple duodenal ulcers have been followed every three months for as long as a year and a half. During this time the peptic-ulcer disease has had the usual remissions and exacerbations. Values of plasma pepsinogen obtained have had moderate variations, always within 10 per cent, however. The fluctuations have in no way been correlated with those in the clinical manifestations of the disease. Likewise, there has been no relation between the plasma pepsinogen level and the severity of peptic ulcer in 1 patient as compared with another. Some of the worst ulcer complications occurred in people with normal plasma values for pepsinogen.

TABLE 1. *Plasma-Pepsinogen Results in Different Conditions.*

GROUP	NO. OF CASES	MEAN LEVEL	STANDARD DEVIATION
		tyrosine units/ml.	
Control	89	486	163
Duodenal ulcer	74	689	193
Subtotal gastrectomy	47	314	93
Gastric ulcer	15	705	293
Gastric carcinoma	5	388	36
Total gastrectomy	5	147	77

Forty-seven patients with duodenal and 7 with benign gastric ulcer have had radical subtotal gastrectomies performed during the period of study. Twelve of these had Billroth I anastomoses (gastroduodenostomy) and 42 had Billroth II procedures (resection with gastrojejunostomy and closure of the duodenal stump). The proximal cuff was similar in all these patients, decision about the type of anastomosis being made at the operating table on the basis of anatomic findings after the specimen had been removed. These patients have had a preoperative base line of at least three plasma pepsinogen determinations and then had their levels followed closely during the immediate postoperative period with less frequent determinations during the outpatient follow-up study. During the first few postoperative days there was great variation in the levels, some individuals immediately manifesting extremely high levels that subsequently fell off to low and others an early drop to low levels.

The data in 9 of these cases were subjected to

*Recently, we explored a patient who proved to have carcinomatosis, secondary to a prepyloric cancer on the lesser curvature. He had free gastric acid, and the plasma pepsinogen was 652 tyrosine units. This value is in the range for benign gastric ulcer and indicates the hazards of over-reliance on a single laboratory determination.

statistical analysis. It was found that there was little change in the mean until the fifth postoperative day, when a statistically significant drop occurred that was sustained during the follow-up period. In the immediate postoperative period there was a striking increase in the standard deviation of these figures. This spread was the greatest on the third postopera-

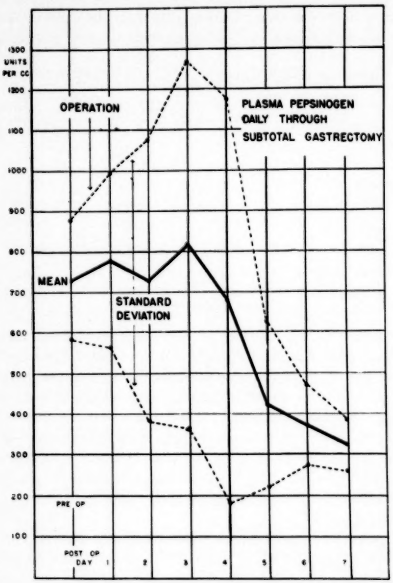


FIGURE 3. *Analysis of Plasma Pepsinogen Results in 9 Patients during the First Week after Subtotal Gastrectomy.*

tive day and then decreased on the fifth day. The results of this analysis are shown in graphic form in Figure 3. These patients have now been followed up to a year and a half. Almost all have maintained low values since operation. A few have had transient increases not correlated with symptoms. To date there have been no proved marginal ulcers but 2 patients in whom that diagnosis was strongly suspected have had low values. There is no difference between the results obtained in the Billroth I anastomosis as compared to the Billroth II.

Four patients after abdominal vagotomy and 1 after thoracic vagotomy have been studied. Only 2 of the former had a marked fall in plasma pepsinogen. After thoracic vagotomy the pepsinogen level fell from a preoperative value of 940 tyrosine units to 450 tyrosine units. This may be an indication of the completeness of the vagotomy. The 1 patient who had abdominal vagotomy with a flat insulin test curve postoperatively had a marked fall in plasma pepsinogen.

Ten patients given therapeutic doses of ACTH or cortisone for diseases not involving the gastrointestinal tract for periods of a week or longer had a mean plasma pepsinogen of 507 tyrosine units, with a standard deviation of 92. This was not significantly different from the normal, in contradistinction to what one would expect from the work of others in this regard with uropepsins.[5]

In an investigation carried out in collaboration with Dr. Seymour Gray's group using normal medical students, gastric pepsin, plasma pepsinogen and uropepsin were studied simultaneously for normal values and to determine the effect of cortisone (175 mg. for seven days) in 2 subjects and compound F (200 mg. for seven days) in 3. The plasma pepsinogen determinations were done in our laboratory, and the gastric pepsin and uropepsin studies in Dr. Gray's. No significant effect of the drugs on the level of uropepsins or plasma pepsinogen was noted. We have tried to correlate plasma pepsinogen levels with gastric pepsin output in several patients before and after operation; however, the results are not satisfactory, presumably because gastric suction after operation is not comparable to preoperative values, owing both to the more rapid emptying and to the alkalinization by bile and pancreatic juices in the gastric cuff. This correlation will have to be done in the laboratory animal.

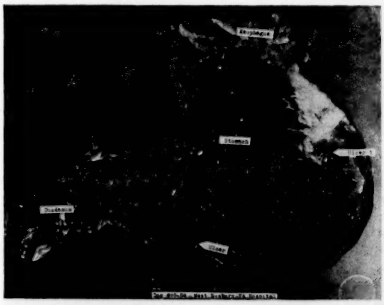


FIGURE 4. *Histamine Ulcer in a Dog.*

Through the kindness of Dr. Lear, of the Thorndike Memorial Laboratory, at the Boston City Hospital, the frozen plasma of 33 patients who were known to have pernicious anemia was submitted for testing. The pepsinogen values were universally low. The range was 50 to 305 tyrosine units, with a mean of 131.8 tyrosine units and a standard deviation of 49 tyrosine units. This is highly significant when compared with the normal and indicates an important diagnostic test for this disease. Four "unknowns" were mixed in with this group of deter-

minations: 1 patient with myxedema, 2 with folic acid deficiency and 1 with iron deficiency. The results, which were respectively 550 tyrosine units, 560 tyrosine units, 375 tyrosine units and 505 tyrosine units, were outside the pernicious-anemia range, and the test was reliable as a differential diagnostic tool. The only other situation in which the pepsinogen is consistently as low is after total gastrectomy. The values in patients with pernicious anemia will overlap those in patients with carcinoma of the stomach, which will always have to be considered in the differential diagnosis.

Laboratory Studies

Basal levels of plasma pepsinogen in the dog correspond with little fluctuation from hour to hour and day to day. Occasionally, very high levels may be noticed. Total and partial gastrectomy and thoracic vagotomy cause a marked and sustained drop. The normal mean is 429 tyrosine units, and that after vagotomy is 270 units.

Attempts to elevate the plasma pepsinogen levels in dogs have largely failed, however. We have created peptic ulcers by histamine[9] (Fig. 4), Ivy

FIGURE 5. *Ulcer in Ivy Gastric Pouch with Antral Transplant to Colon.*

pouches with antral transplants[10] (Fig. 5) and simple antral transplants without affecting the plasma levels (except occasionally in a downward direction). A Mann–Williamson preparation followed for several weeks did not show any change in plasma pepsinogen levels. Vagal stimulation by insulin hypoglycemia[11] over several days and by direct supradiaphragmatic alternating-current stimulation over several hours was without avail. Three dogs showed no change in basal levels when given ACTH for seven days. However, in four preparations with the animals under pentobarbital (Nembutal) anesthesia and being stimulated by intravenous infusions of ACTH over a six-hour period, there was a significant elevation in plasma pepsinogen in gastric venous blood samples as compared with peripheral blood; Figure 6 gives an example of one such experiment. These studies must be extended, for this is the first clue to any success in artificially elevating plasma pepsinogen in dogs.

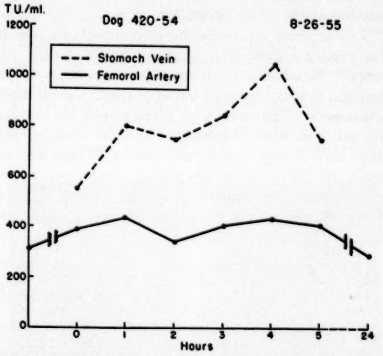


FIGURE 6. *Comparison of Plasma Pepsinogen in Blood from a Stomach Vein of a Dog with Femoral-Artery Blood during the Intravenous Administration of ACTH.*
ACTH was begun at 0 time and continued throughout the experiment. Any difference higher than 100 tyrosine units is significant.

The results reaffirm the fact that experimental canine ulcers correlate poorly in many respects with the natural human variety.

Discussion

The method of measuring plasma pepsinogen described by Mirsky et al.[6,7] has been shown to be reproducible with a coefficient of variation of 4 per cent. There is no apparent change in the proteolytic activity of plasma stored in the frozen state up to a year and a half. The average change in the level of activity from day to day in any subject is about 12 per cent, and the fluctuation throughout the day is in the same range, with no apparent effect secondary to meals.

The average level in a group of control patients without apparent gastrointestinal disease was 486 tyrosine units, with a standard deviation of 163 tyrosine units. Levels in series of patients with duodenal ulcer, gastric ulcer, after subtotal gastrectomy and gastric carcinoma were found to have statistically significant variation from those in the control group. Both ulcer groups were higher than the normal whereas the subtotal-gastrectomy patients were lower. However, there was a wide spread of values in each group, with a resulting overlap of values in all. The mean values in the groups with

gastric and duodenal ulcers were quite close; however, there was a greater standard deviation in the patients with gastric ulcer. It is of great interest that the group with carcinoma of the stomach had a low mean and a small standard deviation of the values so that in spite of its small size it was found that the probability that the difference between it and the normal and ulcer groups was due to chance was less than 1:100 ($P<0.01$).

Two other series would be interesting to quote in this regard. The first, that of Spiro, Ryan and Jones,[12] found in 23 patients with carcinoma of the stomach that the average value of plasma pepsinogen was normal. The second, by Mirsky et al.,[13] reviewed 106 patients with duodenal ulcer, 50 with gastric ulcer and 55 with gastric carcinoma. There was no significant difference in the plasma pepsinogen values between patients with duodenal and gastric ulcers. However, the values in patients with gastric carcinoma were lower:

> [Fifty per cent of the latter] . . . had values which were lower than the lowest of patients with ulcer, while only 15% of those with carcinoma had values which were beyond the mean of the ulcer group. Although a good deal of overlapping occurred, the data suggest that the level of pepsinogen in the serum may serve as an adjunctive aid in distinguishing gastric carcinoma from gastric and duodenal ulcers.

A large group of patients with pernicious anemia had a mean plasma pepsinogen value of 131.8 tyrosine units, with a standard deviation of 49 tyrosine units. These values are quite significant when compared with the normal. The plasma pepsinogen determination is a useful adjunct in the differential diagnosis of this disease.

In the Surgical Research Laboratory plasma pepsinogen has been studied in relation to gastric physiology in the dog. Total gastrectomy, subtotal gastrectomy and vagotomy have been shown to lower the plasma pepsinogen levels significantly. As in the human patient there is little variation from day to day or during the day. We have been largely unsuccessful in artificially elevating the plasma pepsinogen in dogs and have attempted to do this by numerous different ulcer-forming preparations and by direct and indirect vagal stimulation. We have caused transient elevation in the gastric venous blood as compared with the peripheral venous blood by intravenous stimulation of the stomach with ACTH. These studies are being extended.

Conclusions

Plasma pepsinogen is a precursor of pepsin, which is excreted in the urine and determined there as uropepsin.

The laboratory determination of plasma pepsinogen is a reliable and reproducible test and apparently more satisfactory than that for urinary uropepsin.

Plasma pepsinogen remains quite constant after meals and throughout the day.

Plasma pepsinogen levels in patients with peptic-ulcer disease are significantly higher than the normal value, and levels after subtotal gastrectomy are significantly lower than the normal. However, there is overlap in all these groups.

A low plasma pepsinogen in the face of gastric ulceration is a strong indication of cancer. Patients with pernicious anemia will always have a low value, and the differential diagnosis must be made.

Satisfactory vagotomy is followed by a fall in plasma pepsinogen.

Therapeutic doses of ACTH, cortisone and compound F do not affect the plasma pepsinogen level in man.

Experimental ulcer preparations in dogs do not elevate the plasma pepsinogen. Thoracic vagotomy in dogs significantly lowers the pepsinogen level.

Vagal stimulation by insulin hypoglycemia or direct electric impulse will not cause a rise in plasma pepsinogen in dogs.

Intravenous stimulation with ACTH will cause a significant elevation in plasma pepsinogen in gastric venous blood when compared with peripheral blood in dogs.

We are indebted to the Upjohn Company and Winthrop-Stearns, Incorporated, for assistance.

References

1. Gray, S. J., Ramsey, C., Reifenstein, R. W., and Benson, J. A., Jr. Significance of hormonal factors in pathogenesis of peptic ulcer. *Gastroenterology* **25**:156-172, 1953.
2. *Idem.* Clinical use of urinary uropepsin determination in medicine and surgery. *New Engl. J. Med.* **251**:835-843, 1954.
3. Hirschowitz, B. I. Urinary excretion of pepsinogen in gastroduodenal ulceration. *Lancet* **1**:66-69, 1953.
4. Mirsky, I. A., Block, S., Osher, S., and Broh-Kahn, R. H. Uropepsin excretion by man. I. Source, properties and assay of uropepsin. *J. Clin. Investigation* **27**:818-824, 1948.
5. Spiro, H. M., Reifenstein, R. W., and Gray, S. J. Effect of adrenocorticotropic hormone upon uropepsin excretion. *J. Lab. & Clin. Med.* **35**:899-910, 1950.
6. Mirsky, I. A., Futterman, P., Kaplan, S., and Broh-Kahn, R. H. Blood plasma pepsinogen. I. Source, properties, and assay of proteolytic activity of plasma at acid reactions. *J. Lab. & Clin. Med.* **40**:17-26, 1952.
7. Mirsky, I. A., Futterman, P., and Kaplan, S. Blood plasma pepsinogen. II. Activity of plasma from "normal" subjects, patients with duodenal ulcer, and patients with pernicious anemia. *J. Lab. & Clin. Med.* **40**:188-199, 1952.
8. Chinn, A. Studies on blood serum proteolytic enzyme with particular reference to gastric secretory function. *Gastroenterology* **25**:14-23, 1953.
9. Hay, L. J., Varco, R. L., Code, C. F., and Wangensteen, O. H. Experimental production of gastric and duodenal ulcers in laboratory animals by intramuscular injection of histamine in beeswax. *Surg., Gynec. & Obst.* **75**:170-182, 1942.
10. Dragstedt, L. R., Oberhelman, H. A., Jr., Zubiran, J. M., and Woodward, E. R. Antrum motility as stimulus for gastric secretion. *Gastroenterology* **24**:71-78, 1953.
11. French, J. D., Longmire, R. L., Porter, R. W., and Movius, H. J. Extravagal influences on gastric hydrochloric acid secretion induced by stress stimuli. *Surgery* **34**:621-632, 1953.
12. Spiro, H. M., Ryan, A. E., and Jones, C. M. Utility of blood pepsin assay in clinical medicine. *New Eng. J. Med.* **253**:261-266, 1955.
13. Mirsky, I. A., Fisher, B., and Harbison, S. P. Comparison of blood pepsinogen in patients with duodenal and gastric ulcer and patients with gastric carcinoma. *J. Lab. & Clin. Med.* **46**:933, 1955.

CO-OCCURRENCE OF LARGE LEIOMYOMA OF THE ESOPHAGUS AND SQUAMOUS-CELL CARCINOMA OF THE THYMUS*

Report of a Case, with Roentgenologic, Pathological and Clinical Discussion

HOWARD A. FRANK, M.D.,† LEOPOLD REINER, M.D.,‡ AND FELIX G. FLEISCHNER, M.D.§

BOSTON

THIS communication describes two large, unrelated, and uncommon tumors found simultaneously in the mediastinum of a sixty-six-year-old woman. The coincidence is apparently unique, and each tumor is of interest. The first, a leiomyoma of the esophagus as large as any recorded, illustrates the atypical roentgenologic features resulting from an almost entirely extramural direction of growth. The second tumor, a carcinoma of the anterior mediastinum, poses the question of histogenesis of squamous-cell carcinoma arising in this location. Reasons are given for believing that this tumor arose in the thymus. Both tumors were resected successfully.

CASE REPORT

B.R. (B.I.H. 29155), a 66-year-old woman, had been hospitalized 5 times before October, 1951. At the 1st admission, in 1935, for cholecystectomy, a chest film (no longer available for review) was reported as showing enlargement of the cardiac shadow (perhaps because the mediastinal tumor was behind the heart). She was readmitted to the hospital for bronchopneumonia in 1941, when a partially calcified tumor low in the posterior mediastinum was first recognized, in 1943 for a cerebrovascular accident producing permanent hemiplegia and in 1949 for control of diabetes mellitus and paroxysmal tachycardia. A diagnosis of hypertensive and arteriosclerotic heart disease was made, and x-ray study of the chest showed marked widening of the ascending aorta, calcification of the arch of the aorta, fluid in the lower half of the left side of the chest, atelectasis in the left-middle-lung field, and a large soft-tissue mass occupying the posteroinferior mediastinum and extending into the left side of the chest (Fig. 1). This mass had changed little during the preceding 8 years, except for an increase in calcification. The upper half of the stomach was drawn into an esophageal hiatus hernia. In January, 1951, the patient was readmitted to the hospital because of palpitation, weakness, marked emphysema and obesity. For the 1st time a large tumor in the anterior mediastinum, situated above the heart, was seen in the chest film. The specific gravity of the pleural fluid was 1.016. The total protein was 4.3 gm. per 100 ml.; culture, smear and cell block were negative. Surgical investigation was recommended because the newly discovered mediastinal tumor was considered probably malignant, but was delayed owing to the patient's poor general health and lack of symptoms referable to either tumor.

In October, 1951, she was readmitted to the hospital because of increasing pleural effusion, dyspnea, orthopnea and marked fatigue of several days' duration. The anterior mediastinal mass had increased considerably in size and now projected into both the right-lung and left-lung fields (Fig. 2). The findings were otherwise unchanged except for the presence of a thin-walled cavity in the superior segment of the lower lobe of the right lung. There was no cough or sputum, and no dysphagia in spite of displacement of the esophagus nearly to the left anterolateral chest wall. Bronchoscopy showed no invasion of the tracheobronchial system.

At the 1st operation (in November), thoracotomy through the bed of the resected left 8th rib exposed a large quantity of serous pleural fluid, and a large, firm, well circumscribed, bosselated tumor, arising in the posterior mediastinum, displacing the esophagus and mediastinal pleura to the left, spreading the leaves of the pulmonary ligament and displacing the lower lobe of the left lung upward. It extended behind the heart into the right side of the chest. No pleural or pulmonary metastases were observed. The esophagus, vagus nerves and fundus of the stomach occupied a deep cleft in the left anterolateral aspect of the tumor. The tumor was thought to arise from the wall of the esophagus. Its resection required removal of both vagus nerves, the adventitia and muscularis of the esophagus and a portion of the fundus of the stomach. The histological interpretation was fibrosed leiomyoma (Fig. 3). The hiatus hernia was repaired. Several paroxysms of atrial fibrillation occurred in the early postoperative period. Heparin therapy for pulmonary embolism was given during the 3d and 4th weeks after operation. Recovery was otherwise uncomplicated.

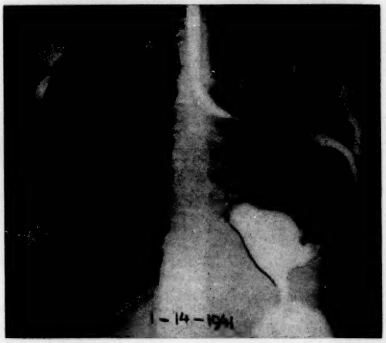


FIGURE 1. *Roentgenogram of the Chest.*

A mass about twice the size of a man's fist is located just behind the heart, to the left of the thoracic spine. In its center are multiple areas of calcification. The esophagus hugs this mass, following its upper left and anterior contour and swinging around the left ventricle anteriorly. About half the stomach is herniated above the diaphragm. No obstruction of the esophagus is noted, and its rugal relief is not grossly distorted.

The patient was discharged for a period of convalescence before anterior thoracotomy. Pleural fluid and dyspnea did not recur. The only complaint on readmission in April, 1952, was foul breath, which was attributed to activation of the chronic lung abscess. The breath odor, infrequent

*From the departments of Surgery, Pathology and Radiology, Beth Israel Hospital and Harvard Medical School.

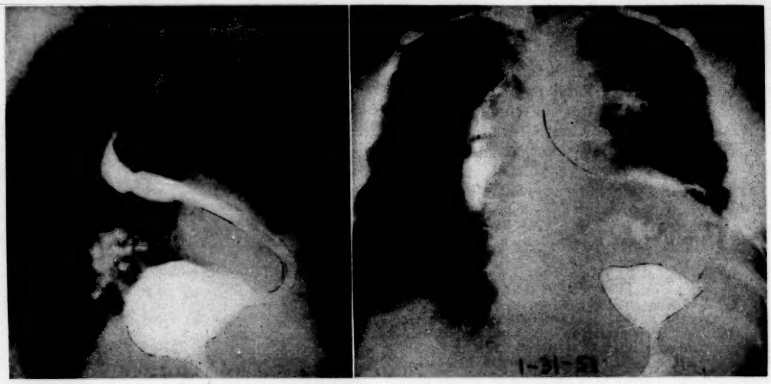
†Assistant professor of surgery, Harvard Medical School; visiting surgeon, associate director of Surgical Service and Senior Ziskind Fellow in Surgery, Beth Israel Hospital.

‡Formerly, clinical associate in pathology, Harvard Medical School, and acting pathologist, Beth Israel Hospital.

§Clinical professor of radiology, Harvard Medical School; director, Department of Radiology, Beth Israel Hospital.

expectoration and a small fluid level in the abscess cavity were eliminated by a 2-week course of penicillin.

At the 2d operation, in April, 1952, the anterior mediastinum was exposed through a transverse incision, which transected the sternum in the 3d interspace. A large, firm, somewhat lobulated and well circumscribed but firmly adherent tumor occupied the area behind the manubrium and extended to the right and the left. Its extirpation required removal of the pericardium over the left pulmonary artery, the left phrenic nerve, the left vagus nerve and the entire length of the left innominate vein. The pathological diagnosis was "squamous-cell carcinoma" (Fig. 4-7). Convalescence was uneventful apart from several brief bouts of atrial fibrillation.



A B

FIGURE 2. *Lateral* (A) *and Posteroanterior Views* (B) *of the Chest.*
The tumor in the upper mediastinum is located anteriorly and does not impinge on the trachea or esophagus. It has increased in size substantially in the past eighteen months. The centrally calcified lower tumor in the posterior mediastinum displaces the esophagus to the left anteriorly.

In the subsequent 4 years, the patient has been free of chest discomfort, pleural fluid and dyspnea. The cavity in the right lower lobe has caused no difficulty. X-ray examinations of the chest have shown no recurrence of the mediastinal tumor and no metastases. No evidence of myasthenia gravis has been observed. She does her housework, but her general activity is limited, as before operation, by obesity and residual hemiplegia.

DISCUSSION

Roentgenologic Considerations

Roentgenologic interest centers in the tumor of the lower posterior mediastinum, the leiomyoma of the esophagus. The esophagus is the least common location in the gastrointestinal tract for leiomyomas in general[1] and a particularly uncommon location for myomas with marked calcification. A similar lesion, at first thought to be a mass of calcifying lymph nodes, has been reported.[2] Spindle-cell tumors of the gastrointestinal tract in general are not often calcified, although the larger the tumor, the greater the likelihood of central necrosis and calcification. Among 269 leiomyomas and leiomyosarcomas of the alimentary tract observed at the Mayo Clinic only 5 were found to be calcified,[3] and an earlier roentgenologic review of leiomyomas of the esophagus disclosed only 4 that were calcified.[4]

The usual leiomyoma of the esophagus is an "intramural, extramucosal tumor," described roentgenologically by Schatzki and Hawes[5] as a tumor that originates within the wall, projects into the lumen and shows abrupt upper and lower edges in profile view. Virchow[6] and Anitschkow[7] recognized "internal" and "external" leiomyomas of the alimentary tract. Baker and Good[8] amplify this classification to include small, entirely intramural tumors, usually not demonstrable by roentgen examination; polypoid tumors; sessile tumors projecting into the lumen — the "intramural, extramucosal tumors"; dumbbell tumors, roentgenologically like the sessile tumors but extending outward so that a major part of the tumor mass lies external to the esophagus; and external tumors without projection into the lumen. The lesion reported above was of the last variety. These tumors are identical histologically. The direction of growth may be fortuitous or may reflect an origin from the muscularis mucosae for the intramural and intraluminal lesions, and from the muscularis propria for the external tumors. Thus, large external leiomyomas may be resected without injury to the mucous membrane. The mucosal surface is smooth even when the tumor projects into the lumen. The deep mucosal ulcer so common in leiomyomas of the stomach and duodenum does not occur in the esophagus.

The largest leiomyomas of the esophagus are usually found in its lowermost portion. Some extend into the stomach. Many have a horseshoe or thyroid

shape. The mucosa may be drawn into a diverticulumlike dimple, but the lumen is rarely narrowed. In the case presented above, upward traction on the stomach by the enlarging esophageal tumor probably accounted for the hiatus hernia.

Pathological Considerations

The pathologist's interest centers upon the histogenesis of the anterior mediastinal tumor. Microscopical examination revealed a tumor divided by stout, densely collagenized and poorly vascularized septums into primary nodules, 1 cm. or more in diameter. These nodules were composed of many discrete epithelial islands varying in size and configuration, supported by a moderately fibrillar and vascular stroma. The epithelial cells were of two types. Type 1 cells, at the periphery of the epithelial islands, were basal in appearance and had indistinct cell borders, scanty, pale eosinophilic and frayed cytoplasm, and elongated, stippled, richly chromatic nuclei. Mitotic figures were sparse. The marginal Type 1 cells were aligned along delicate strands of intertwining stroma to form trabecular and short pinwheel patterns (Fig. 5).

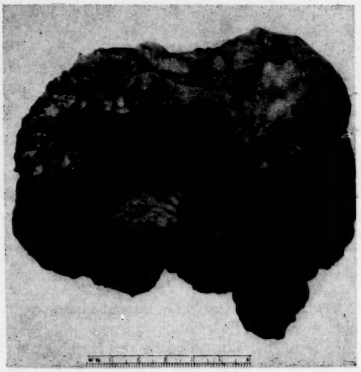


FIGURE 3. *Tumor of the Posterior Mediastinum after Fixation (S51-3066).*

When fresh, the mass weighed 3500 gm. and measured 35 x 20 x 12 cm. Its configuration suggests a giant thyroid gland — that is, two lateral masses of roughly equal size connected by an isthmus forming a deep anterior groove, which furnishes a bed for the esophagus, the vagus nerves and the upper fundus of the stomach. The mass was of firm consistence, nearly incompressible and enclosed by a delicate capsule. Its cut surface was compact, whorly and fibrous. Microscopical examination revealed a largely hyalinized spindle-cell tumor, interpreted as a fibrosed leiomyoma.

The central portions of the epithelial islands were composed of larger squamous Type 2 cells. These had distinct borders, polygonal contours, compact cytoplasm and intercellular bridges (Fig. 6). Their nuclei were generally larger, more rounded and less chromatic than those of Type 1 cells, and nucleoli were more frequent. No mitotic figures were found. These cells were aggregated into well defined spherical or ovoid masses and pearls, situated eccentrically within the epithelial islands (Fig. 6). At the centers of these aggregates, shrunken necrobiotic cell clumps were found, some incrusted with calcium salts and others liquefied so as to form cysts of gross and microscopical dimensions (Fig. 7).

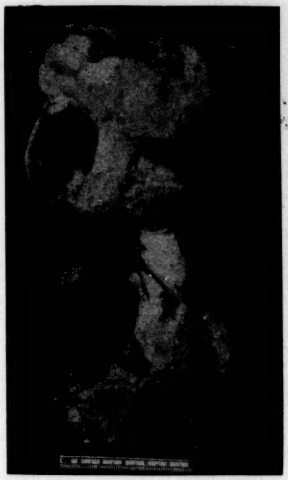


FIGURE 4. *Tumor of the Anterior Mediastinum.*

The mass weighed 203 gm. and measured 10 x 9 x 5.5 cm. It was ovoid and well circumscribed, but only partially encapsulated. Tags of fibrous and adipose tissue, pericardium, an innominate vein and segments of phrenic and vagus nerve were attached. A solitary cyst, 6 cm. in longest dimension, occupied approximately a third of the mass. Its lining was smooth, glistening, yellowish tan and mottled by ecchymoses. The cyst contents were watery, thin and bluish red. The solid portions of the mass were unyielding and of nearly cartilagenous consistence. The cut surface disclosed discrete rounded or irregularly confluent nodules, varying in diameter from one to several centimeters, demarcated by stout, glistening white fibrous-tissue septums. The nodules were composed of delicate tan strands of smooth texture, which intertwined closely with a yellowish, dry, granular tissue, punctuated by a multitude of minute cysts, 0.1-0.3 cm. in diameter, filled with thick, turbid, brownish fluid.

Vascular invasion by epithelial elements was not demonstrated. Two anthracotic lymph nodes on the surface of the tumor were not involved. No residues of normal thymus were found in or about the neoplasm.

Neither at operation nor during a four-year follow-up period was there any evidence that this tumor had metastasized from elsewhere. It is interpreted, therefore, as a primary carcinoma, of a low grade of malignancy, arising in the anterior mediastinum and dis-

playing both basal and squamous features, including prickle cells. Its origin may be considered either teratogenic or thymogenic. The epithelial component of malignant teratomas of the anterior mediastinum usually appears as a poorly differentiated adenocarcinoma.[9] When squamous-cell carcinoma does develop, it is found as part of a complex lesion or else in association with recognizable residua of the dermoid cyst from which it derived.[10] No trace of pre-existing dermoid cyst or dermal adnexa was found in the present tumor. Its stroma was adult connective tissue.

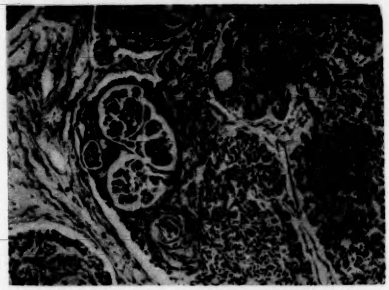


FIGURE 5. *Section of the Tumor of the Anterior Mediastinum, Showing Several Epithelial Islands (X90). The periphery of the epithelial islands is composed of small, Type 1 cells, which are seen here predominantly in trabecular patterns. The squamous Type 2 cells form defined aggregates and contain necrobiotic compartments filled with clumps of shrunken cells and enveloped by viable Type 2 cells in concentric arrangement.*

FIGURE 6. *Section of the Tumor of the Anterior Mediastinum, Showing a Squamous Aggregate with Intercellular Spines Sharply Delineated against the Surrounding Type 1 Cells and with the Marginal Type 2 Cells Compressed (Hematoxylin and Eosin Stain X325).*

Embryologic and anatomic evidence supports the view that squamous-cell carcinoma may arise from the thymus. The thymic primordia are considered to derive from the entoderm of the third pharyngeal pouch, in close association with the gill plate.[11] A separate ectodermal component added by the gill furrows perhaps gives rise to Hassall's corpuscles in the developed thymus.[12] Hassall's corpuscles closely resemble epidermoid pearls,[13] and this may have a bearing on the prickle-cell differentiation in the tumor reported above. The pearly structures of the present tumor, the Hassall corpuscles of a normal thymus and the pearls of an epidermoid carcinoma of the skin reacted similarly to histochemical tests for protein-bound sulfhydryl and disulfide groups[14] (Fig. 8). Injection of tar into guinea pigs is said to cause transformation of Hassall's corpuscles into cornifying squamous epithelium.[15]

However, an ectodermal component in the formation of the thymus need not be assumed to account for the development of squamous-cell carcinoma in that organ. The lesion occurs in the pharynx, a purely entodermal derivative closely related embryologically to the thymus. The relation between pharynx and thymus is further illustrated by the lymphoepitheliomas, unique to these two tissues.[16] Squamous-cell nests with occasional prickle cells have been found in an otherwise typical lymphoepithelioma of the thymus associated with myasthenia gravis.[17] Squamous-cell features observed occasionally in non-neoplastic thyroid glands and in thyroid carcinomas may similarly reflect the origin from pharyngeal pouches.

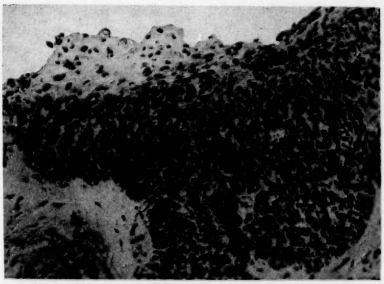


FIGURE 7. *Wall of a Macroscopic Cyst from the Tumor of the Anterior Mediastinum, Showing an Inner Layer of Type 2 Cells Resting on Type 1 Cells Arranged in Trabeculae and Ill Defined Pinwheels (Hematoxylin and Eosin Stain X65).*

A few other cases of prickle-cell-containing carcinoma considered to arise in the thymus have been reported.[18,19] The pearly structures within these tumors may be interpreted as metaplastic thymic epithelium[20] or, perhaps, as neoplastic Hassall corpuscles.[21]

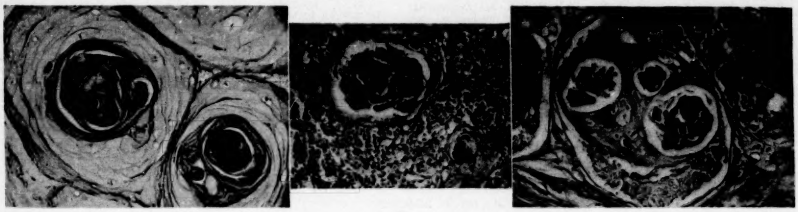
In summary, although a teratogenic derivative cannot be ruled out, we believe that the squamous-cell carcinoma reported here arose from the thymus.* It has been argued that teratomas of the thymus are

*Castleman[22] concurs with this interpretation and has included the present case in his monograph.

not derived from germ cells but are the result of faulty embryogenesis.[9] If this view is accepted, there is little reason to attempt to distinguish between the inherent potentialities of the thymic anlage versus the inclusion of branchial elements as the basis for squamous-cell differentiation in thymic tumors.

These two lesions developed coincidentally within the same mediastinum — an important point because long awareness of the presence of the leiomyoma led to some delay in recognizing that the second tumor was unrelated and malignant.

The easy removal of the very large leiomyoma, and



A B C

FIGURE 8. *Sections Stained for the Demonstration of Protein-Bound Sulfhydryl and Disulfide Groups*[14] *(X100), Showing Pearls* (A) *from an Epidermoid Carcinoma of the Ankle (S53-795), Two Hassall Corpuscles* (B) *from the Normal Thymus of a Twenty-three-Year-Old Woman (S53-900) and Pearl-like Configuration* (C) *from the Tumor of the Anterior Mediastinum Reported in This Paper (52-1166).*

Clinical Considerations

The clinical features of leiomyoma of the esophagus have been presented in several recent reviews.[23-25] The patient described above was not aware of any dysphagia in spite of the large size of the tumor and the marked displacement of the esophagus. However, the development of a lung abscess may be taken as evidence of esophageal dysfunction.

The advanced cardiovascular disease and the late appearance of symptoms that could be related to the tumors delayed surgical treatment. The transverse incision across the sternum gave excellent exposure of the tumor in the anterior mediastinum and very little postoperative discomfort. Fortunately, little respiratory disturbance resulted from the resection of the phrenic nerve and recurrent laryngeal nerve on the left. No venous distention of the head or upper extremity followed resection of the innominate vein. Resection of carcinoma of the thymus involving an innominate vein has been reported,[26] but in most cases primary carcinomas arising in the mediastinum are not resectable.[27-29] When resection of carcinoma of the thymus can be accomplished, recurrence is uncommon.[26,30,31] Radiation therapy is less satisfactory,[30] but, guided by biopsy, may be helpful when resection cannot be done.[32,33]

Summary

The radiologic appearance of a large leiomyoma of the lower esophagus, with extensive calcification and virtually completely extramural direction of growth, is described, and the gross and microscopical morphology of an unusual primary squamous-cell carcinoma of the anterior mediastinum, presumably arising in the thymus, is discussed.

the successful removal of the carcinoma attached to pericardium, phrenic and vagus nerves and innominate vein in a sixty-six-year-old, obese and emphysematous woman with diabetes mellitus and hypertensive and arteriosclerotic cardiac and cerebral disease is reported.

References

1. Piacentini, L. Leiomyoma of esophagus. *J. Thoracic Surg.* **29**: 296-316, 1955.
2. Case Records of the Massachusetts General Hospital (Case 38261). *New Eng. J. Med.* **246**:1015-1017, 1952.
3. Good, A., and Baker, J. L. Personal communication.
4. Pape, R., and Spitznagel. Myomas of esophagus. *Radiology* **17**: 570, 1931.
5. Schatzki, R., and Hawes, L. E. Roentgenological appearance of extramucosal tumors of esophagus: analysis of intramural extramucosal lesions of gastrointestinal tract in general. *Am. J. Roentgenol.* **48**:1-15, 1942.
6. Virchow, R. *Die krankhaften Geschwülste: Dreissig Vorlesungen, gehalten während des Wintersemesters 1862-1863 an der Universität zu Berlin.* Vol. 3. Berlin: A. Hirschwald, 1863-1867. P. 107.
7. Anitschkow, N. N. Zur Lehre der Fibromyome des Verdauungskanals: über Myome des Ösophagus und der Kardia. *Virchows Arch. f. path. Anat.* **205**:443-452, 1911.
8. Baker, H. L., Jr., and Good, C. A. Smooth-muscle tumors of alimentary tract: their roentgen manifestations. *Am. J. Roentgenol.* **74**:246-255, 1955.
9. Schlumberger, H. G. Teratoma of anterior mediastinum in group of military age: study of sixteen cases and review of theories of genesis. *Arch. Path.* **41**:398-444, 1946.
10. Houghton, J. D. Malignant teratoma of mediastinum: report of case and review of 24 cases from literature. *Am. J. Path.* **12**:349-372, 1936.
11. Patten, B. M. *Human Embryology.* 776 pp. Philadelphia: Blakiston, 1945.
12. Norris, E. H. Cited by Schlumberger.[9]
13. Bargmann, W. Der Thymus. In *Handbuch der Mikroskopischen Anatomie des Menschen.* Edited by W. v. Möllendorff. Vol. 6. Berlin: Springer, 1943. Pp. 1-172.
14. Barrnett, R. J., and Seligman, A. M. Histochemical demonstration of protein-bound sulfhydryl groups. *Science* **116**:323-327, 1952.
15. Okamuro, T. Cited by Bargmann.[13]
16. Kettle, E. H. *Pathology of Tumors.* Revised and rewritten by W. G. Barnard and A. H. T. Robb-Smith. Third edition. 318 pp. New York: Hoeber, 1946.
17. Wu, T. T. Lymphoepithelioma of thymus. *J. Path. & Bact.* **41**: 351-366, 1935.
18. Ambrosini, G. De l'épitheliome du thymus. No. 344. 60 pp. Paris thesis, 1894.
19. Strauss, S. G. Malignant neoplasms of thymus. *New York State J. Med.* **110**:646, 1919.
20. Wilson, F. N., and Pritchard, J. E. Malignant thymoma. *Canad. M. A. J.* **53**:444-454, 1945.

21. Foot, N. C. *Identification of Tumors: Essential gross and microscopic pathologic features systematically arranged for easier identification.* 397 pp. Philadelphia: Lippincott, 1948.
22. Castleman, B. Tumors of thymus gland. In *Atlas of Tumor Pathology.* Section V. Fascicle 19. Washington, D. C.: Armed Forces Institute of Pathology, 1955. P. 37 (Fig. 30).
23. Sweet, R. H., Soutter, L., and Valenzuela, C. T. Muscle wall tumors of esophagus. *J. Thoracic Surg.* **27**:13-35, 1954.
24. Boyd, D. P., and Hill, L. D., III. Benign tumors of esophagus. *Ann. Surg.* **139**:312-324, 1954.
25. Lewis, B., and Maxfield, R. G. Leiomyoma of esophagus: case report and review of literature. *Internat. Abstr. Surg.* **99**:105-128, 1954.
26. Burnett, W. C., Rosemond, G. P., and Bucher, R. M. Symposium on safeguards in surgical diagnosis: diagnosis of mediastinal tumors. *S. Clin. North America* **32**:1673-1694, 1952.
27. Heuer, G. J., and Andrus, W. DeW. Surgery of mediastinal tumors. *Am. J. Surg.* **59**:146-224, 1940.
28. Blades, B. Mediastinal tumors: report of cases treated at Army thoracic surgery centers in United States. *Ann. Surg.* **123**:749-765, 1946.
29. Thompson, J. V. Collective review: mediastinal tumors and cysts. *Internat. Abstr. Surg.* **84**:195-221, 1947.
30. Seybold, W. D., McDonald, J. R., Clagett, O. T., and Good, C. A. Tumors of thymus. *J. Thoracic Surg.* **20**:195-215, 1950.
31. Key, J. A. Mediastinal tumors. *S. Clin. North America* **34**:959-978, 1954.
32. Binkley, F. M., Thorburn, J. D., Stephens, H. B., and Grimes, O. F. Mediastinal tumors of thymic origin. *California Med.* **78**: 267-273, 1953.
33. Effler, D. B. Thymic tumors. *J. Thoracic Surg.* (in press).

PERNICIOUS ANEMIA DUE TO DIETARY DEFICIENCY OF VITAMIN B_{12}*

MYRON POLLYCOVE, M.D.,† LEONARD APT, M.D.,‡ AND MARVIN J. COLBERT, M.D.§

With the Technical Assistance of Mary Pratt, M.A., Joan Donovan, B.S., Jack Sullivan, B.S., and Thomas Giaveniello, B.S.

BOSTON

PERNICIOUS anemia is a deficiency state resulting from a lack of vitamin B_{12}. This lack usually occurs as a result of an inability to absorb the vitamin from the intestinal tract because of the absence of a specific factor, present in normal gastric juice, known as the intrinsic factor of Castle.[1,2]

An optimal, well balanced diet contains 8 to 15 microgm. of vitamin B_{12} per day.[3,4] A daily parenteral dose of 1 microgm. induces and maintains a complete remission in patients with pernicious anemia.[5,6] It thus appears probable that only a small fraction of the normal dietary intake need be absorbed to meet body requirements for this substance. In the case reported below a severe macrocytic anemia, with a megaloblastic bone marrow, developed after the patient had scrupulously avoided all foods of animal origin for at least eight years. The observations recorded below indicate that the pernicious anemia occurred largely, if not solely, as a result of dietary vitamin B_{12} deficiency.

TABLE 1. *Laboratory Data.*

Hospital Day	Urine	Red-Cell Count	Hemoglobin	Hematocrit	Mean Corpuscular Volume	Mean Corpuscular Hemoglobin	Mean Corpuscular Hemoglobin Concentration	Reticulocytes	Platelets	White-Cell Count	Segmented Neutrophils	Band Forms	Eosinophils	Lymphocytes	Bilirubin	Total Protein	Albumin	Globulin
		X10⁶	*gm./ 100 ml.*	%	*cu. microns*	*micro-microgm.*	%	%	*per cu. mm.*	*X10³*	%	%	%	%	*mg./ 100 ml.*	*gm./ 100 ml.*	*gm./ 100 ml.*	*gm./ 100 ml.*
1	Normal	0.65*	2.7*	9	139	42	30	2*	16,000	14.6	82	1	1	16	3.4	4.6	2.7	1.9
5	Normal									13.1					2.7			
7	Normal									10.9								
14	Normal									12.8					1.6			
18										12.1								
30	Normal									10.6						5.6	2.8	2.8
42										13.0					0.9			
63	Normal									12.2					0.6			
84	Normal									11.5					0.8			

*Values on succeeding days shown in Fig. 1.

*From the Medical Service, Radioisotope Unit and Research Laboratory, Boston Veterans Administration Hospital, and the Department of Medicine, Tufts University School of Medicine.

†Research associate, Donner Laboratory, University of California, Berkeley, California; formerly, teaching fellow in medicine, Tufts University School of Medicine, and resident in medicine, Medical Service, Boston Veterans Administration Hospital.

‡Formerly, staff physician, Radioisotope Unit, Boston Veterans Administration Hospital.

§Formerly, resident in medicine, Medical Service, Boston Veterans Administration Hospital.

Case Report

J.D.M., a 60-year-old single, unemployed man of Scotch descent, entered the Boston Veterans Administration Hospital on February 25, 1954, in stupor. The history was obtained from his sister. No member of his family was known to have had pernicious anemia. He had had intermittent ankle edema for 6 years. Alcoholism was denied. He had received no drugs in recent years. Thirty years before admission he had been troubled considerably with dermatitis, particularly of the hands and feet. This dermatitis was cured when he was started on "a cleansing diet followed by a building diet." He ceased to work in 1929 (at the age of 35) "because he was delicate." In 1932 he "heard voices" but was not sent to an institution or treated. In 1945 his only brother died of a cerebral hemorrhage. There appeared to be a change in his behavior at this time. He was admitted to the Boston Psychopathic Hospital and was discharged after 7 days. He was readmitted a year later after hearing voices and talking to himself. In this hospital he consistently refused to eat animal products or dairy products in any form. He subsisted on vegetables and fruits, which his sister supplied for his entire year in the hospital. On October 29, 1947, he was transferred to another mental hospital, where the record confirmed his avoidance of "meat and flesh." After another year in the hospital he was discharged to the care of his sister with a final diagnosis of "schizophrenic reaction, paranoid type, chronic, severe, manifested by delusional ideas, auditory hallucinations, distrust, inappropriate affect, and unco-operativeness." After release from the hospital, he continued his eating habits unchanged and steadfastly declined all not of feces for 24 hours before entry and had passed a normal brown stool as recently as the morning of entry. At no time had there been any vomiting, diarrhea, melena or hematemesis.

Before his obvious failing during the weeks before admission, his typical diet was as follows: for breakfast, stewed, fresh or canned fruit, coffee with sugar but no cream, and 2 or 3 slices of toast; in the mid-morning, fruit juice or figs; for lunch, 4 different cooked vegetables (1 of these being potatoes), all covered with olive oil, 3 pieces of bread with peanut butter, jelly or soya butter — usually the last — tea and, for dessert, peaches or apricots; in midafternoon, a banana or orange; and for supper, asparagus on toast or lima beans, 2 pieces of bread, tea and, for dessert, stewed fruit or apple sauce. Alcoholism was denied.

Physical examination showed an emaciated, stuporous man who was remarkably pallid, with a faded lemon-yellow complexion. He breathed slowly and deeply and responded feebly to painful stimuli. A few petechiae, but no ecchymoses, were noted on the skin. There was slight pitting edema of the entire body. The conjunctivas were extremely pale, and bilateral conjunctival exudate was present. There was slight scleral icterus. Bilateral retinal hemorrhages were present. The tongue was dry and coated; it had petechiae on its undersurface, and was somewhat smooth at the edges. The thoracic cage was unduly prominent. The lungs were clear except for a few crepitant rales at the bases. The pedal pulses could not be felt, but the other peripheral pulses were easily palpable. The heart was not enlarged. The rhythm was regular and the rate slow. The aortic 2d sound was louder than the pulmonic. There was

Table 1 *(Concluded).*

Hospital Day	Fibrinogen	Uncorrected Sedimentation Rate	Prothrombin Time	Cephalin Flocculation	Thymol Turbidity	Serum Cholesterol	Cholesterol Esters	Serum Sodium	Serum Potassium	Carbon Dioxide	Serum Calcium	Serum Inorganic Phosphorus	Serum Uric Acid	Urinary 17-Ketosteroids	Urinary 11-Oxysteroids	Serum Iron	Residual Iron-Binding Capacity	Total Iron-Binding Capacity	Serum Vitamin B_{12}
	mg./100 ml.	*mm./hr.*	*sec.*			*mg./100 ml.*	*mg./100 ml.*	*milli-equiv./liter*	*milli-equiv./liter*	*milli-equiv./liter*	*mg./100 ml.*	*mg./100 ml.*	*mg./100 ml.*	*mg./24 hr.*	*mg./24 hr.*	*micro-gm./100 ml.*	*micro-gm./100 ml.*	*micro-gm./100 ml.*	*micro-micro-gm./100 ml.*
1	75	0	47.0	++++ in 24 hr.	Normal	94	59	144	6.5	15.6	7.6	5.7	10.5						70
5								130	4.0	21.0	7.5			2.26	3.6				
7											7.7		4.0						
14	112	12	26.0									2.2							
18			18.0													114*	300*	414*	
30		9	13.5	++ in 48 hr.	Normal														
42			14.0					137	4.2	25.4	7.8	2.0							
63	245		13.0			135	24												
84	330	8	14.0	+ in 48 hr.	Normal			138	4.2		7.7								

*Values on succeeding days shown in Fig. 1.

medical care. In 1951 he had a severe infection of the respiratory tract. At that time a physician visited him at home, administered 4 injections of penicillin and also advised injections of liver extract. The patient refused to receive this animal product. In 1953 he became bed ridden, allegedly because of weakness and pain in the lower extremities. His sister began surreptitiously crushing vitamin tablets and incorporating them into his vegetables and fruit. On this treatment he improved and again became ambulatory. He weighed 52.1 kg. (115 pounds) 1 year before admission. During the months before admission he gradually became weaker, ate less and less, and finally became stuporous. He had been incontinent of urine but a Grade 1 blowing systolic aortic murmur that was well transmitted into the right side of the neck. No abdominal organs or masses were palpable. Rectal examination revealed a brown, formed stool. The guaiac test for blood in the stool was negative. At this time he appeared to have moderate, bilateral foot drop, but later examination, after improvement, showed foot drop on the right only. Neurologic examination revealed profound weakness. Complete sensory examination at this time was not possible but seemed to be negative on later examination, though he did not co-operate fully. At no time during the hospital course was it possible to detect impairment of the posterior or lateral spinal column.

The temperature was 99°F. by rectum, the pulse 60, and the respirations 16. The blood pressure was 56/40.

The laboratory data are presented in Table 1. The peripheral blood film and a bone-marrow-aspiration smear taken on admission had all the classic morphologic changes described in pernicious anemia with the exception of leukopenia. Examination of a bone-marrow-aspiration smear performed on the 21st hospital day revealed moderate normoblastic hyperplasia of the erythroid series.

The gastric juice had ample free acid. The serum vitamin B_{12} immediately after entry was 70 micromicrogm. per milliliter, which is in the range observed in patients with pernicious anemia. Studies of vitamin B_{12} absorption employing oral doses of radioactive vitamin (Co^{60}-labeled vitamin B_{12}) were performed. The methods, results, and interpretation of these determinations are discussed below.

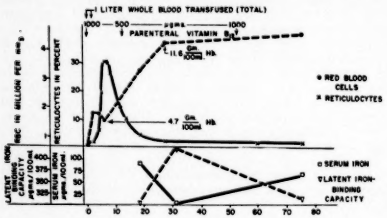


FIGURE 1. *Response of Erythrocytes, Serum Iron and Latent Iron-Binding Capacity to Vitamin B_{12} in a Patient with Dietary Pernicious Anemia.*

Radiographic examination of the chest demonstrated emphysema and possibly bronchiectasis.

On entry to the hospital an electrocardiogram disclosed low voltage, 1st-degree atrioventricular block, a prolonged QT interval and ST-segment and T-wave changes. These were interpreted as consistent with severe malnutrition. On the 10th and 19th hospital days the electrocardiograph tracings were not remarkable except for low voltage. On the 28th hospital day there were ST-segment and T-wave changes suggesting ischemia or pericarditis. Hypertrophy and strain of the left ventricle, digitalis effect and 1st-degree atrioventricular block were noted in the last electrocardiographic tracing on the 49th hospital day.

Because of the patient's precarious condition, multiple-vitamin therapy was begun 2½ hours after entry. An infusion of isotonic saline solution was started intravenously, and 500 microgm. of vitamin B_{12}, 15 mg. of folic acid, 500 mg. of vitamin C, 75 mg. of vitamin K, 10 mg. of thiamine, 10 mg. of riboflavin, 5 mg. of pyridoxine, 50 mg. of calcium pantothenate and 250 mg. of niacin were given intravenously. After this, 1 unit of whole blood was administered slowly. On the same night he received 500 microgm. of vitamin B_{12} and 15 mg. of folic acid intramuscularly. He was put in an oxygen tent. On the day after entry he was given a 2d unit of whole blood. No more transfusions were given during the hospital stay. On the morning after entry he answered simple questions and was irritable. He was then able to take fluids by mouth, choosing fruit juices and ginger ale, and refusing dairy products. Over the course of 10 days the blood pressure gradually rose to 120/60, remaining at this level throughout the hospital stay. He was fairly co-operative until the 8th hospital day, when he refused examination, injection and food. Psychiatric opinion was that he had schizophrenia of the paranoid type. The retinal hemorrhages cleared within a few days of entry and did not recur. Throughout the hospital course he was given infrequent but massive parenteral doses of vitamin B_{12} totaling approximately 3000 microgm. over 85 days. An average of 60 mg. of folic acid was given orally each day during the 1st 4 weeks in the hospital and discontinued thereafter. Only vitamin B complex and vitamin K tablets were continued during the remainder of the hospital stay.

About 3 weeks after entry, the patient had a spontaneous subconjunctival hemorrhage on the right that cleared gradually over the next few days. Although the edema was minimal on admission within 2 weeks marked pitting edema of the lower extremities and moderate pitting edema of the hands developed. This gradually subsided when dietary salt was restricted and digitoxin was administered. The digitoxin was continued throughout most of his hospital stay. On the 21st hospital day the circulation time (Decholin method) was 15 and 16 seconds on 2 tests. Throughout the entire hospital course he refused to ingest any animal or dairy products. During the latter part of his hospital stay, the edema and dyspnea subsided, and he was able to do a small amount of walking without distress. Shortly before discharge he appeared much more alert and cheerful. He was weighed twice during his hospital stay; he weighed 32.7 kg. (72 pounds) on the 49th and 35.8 kg. (79 pounds) on the 84th hospital day.

METHODS AND RESULTS

Hematologic Response

The patient's response to vitamin B_{12} and nutritional therapy is shown in Figure 1. The maximal reticulocyte count of 30 per cent was obtained on the sixth and seventh days after therapy was begun. The red-cell count rose steadily from a post-transfusion level of 1,500,000 (650,000 before transfusion) to 4,200,000 during a three-week period. The platelet count, as determined by the direct method, paralleled the red-cell count, rising from 16,000 to 175,000 during the three-week period. This reaction is characteristic of an optimal response to antipernicious-anemia therapy.[7]

Serum Iron and Iron-Binding Capacity

Serum iron determinations were obtained by a modification of the method of Kitzes, Elvehjem and Schuette,[8] the normal range being 70 to 170 microgm. per 100 ml. Latent iron-binding capacity was determined by the method of Rath and Finch,[9] the normal range being 200 to 300 microgm. per 100 ml., the associated saturation of total iron-binding capacity being 25 to 40 per cent. The values obtained are shown in Figure 1. Two and a half weeks after therapy was instituted the serum iron was 114 microgm. per 100 ml., with 28 per cent saturation. During the next weeks the serum iron level dropped to 26 microgm. per 100 ml., with an associated latent iron-binding capacity of 425 microgm. and a total iron-binding capacity of 451 microgm. per 100 ml., and 5.8 per cent saturation. During the following weeks the serum iron rose to 84 microgm. and the latent iron-binding capacity fell to 310 microgm. and the total iron-binding capacity to 394 microgm. per 100 ml., with 21.3 per cent saturation.

Serum Vitamin B_{12}

The serum vitamin B_{12},* determined immediately after entry and before any therapy, was 70 micromicrograms per milliliter.

*Assay performed by Dr. Arnold A. Lear and his associates at the Thorndike Memorial Laboratory, Boston. With the *Euglena gracilis* bioassay method, the normal range is 300 to 800 micromicrogm. per milliliter.[10,11]

Vitamin B_{12} Absorption

The details, interpretation and evaluation of the methods used to determine vitamin B_{12} absorption are presented elsewhere.[12] Radioactive vitamin B_{12} was given by mouth on the twenty-fifth and fifty-third hospital days. During the ten-day period after the first oral dose of 0.5 microgm. of cobalt^{60}-labeled vitamin B_{12} the fecal elimination of the radioactive vitamin and hepatic deposition of cobalt^{60} were determined simultaneously. After the second oral dose of 2.0 microgm. of cobalt^{60}-labeled vitamin B_{12}, given simultaneously with a subcutaneous injection of 1000 microgm. of nonradioactive vitamin, a twenty-four-hour collection of urine was analyzed for excretion of the radioactive vitamin. The results obtained are shown in Table 2 and Figures 2, 3 and 4. The fecal elimination of radioactive vitamin B_{12} was 38 per cent. This value is within the range of values obtained in normal persons in contrast to the high percentages of orally administered vitamin B_{12} eliminated in the feces of subjects with pernicious anemia in remission (Fig. 2). The normal intrinsic-factor potency of the patient's gastric juice is demonstrated by its capacity to reduce to normal the abnormally high fecal elimination of orally administered B_{12} of subject G.A. with pernicious anemia in remission. The simultaneously determined hepatic deposition of cobalt^{60} was 4500 counts per minute per microcurie ingested (0.12 microcurie associated with the ingested 0.5 microgm. of cobalt^{60}-labeled vitamin B_{12}). This value is within the normal range and is in contrast to the very low counting rates obtained in subjects with pernicious anemia in remission (Fig. 3). Again the normal intrinsic-factor activity of the patient's gastric juice was demonstrated by its ability to raise the hepatic deposition of cobalt^{60} in subject G.A., with pernicious anemia in remission, to a normal level. The twenty-four-hour urinary excretion of radioactive vitamin B_{12} was 12 per cent of the oral dose. This value is within the normal range and contrasts with the very low percentages excreted by subjects with pernicious anemia in remission (Fig. 4).

TABLE 2. *Elimination, Excretion and Absorption of Orally Administered Vitamin B_{12}.*

SUBJECT	NO. OF SUBJECTS	PERCENTAGE OF COBALT^{60}-LABELED VITAMIN B_{12} ELIMINATED IN FECES*	PERCENTAGE OF COBALT^{60}-LABELED VITAMIN B_{12} NOT ELIMINATED IN FECES*	DEPOSITION OF COBALT^{60} IN LIVER	PERCENTAGE OF COBALT^{60}-LABELED VITAMIN B_{12} EXCRETED IN URINE†
				cpm/microcurie	
J.D.M.	1	37	63	4500	12.2
Normal persons	8	18-47	53-82	3360-5300	6.9-13.8
Patients with pernicious anemia	5	81-97	3-19	171-769	0.3-1.0
Patient with pernicious anemia (G.A.) & J.D.M. (gastric juice)	1	48	52	2713	
Patients with pernicious anemia & normal persons (gastric juice)	5	36-50	50-64	2541-3495	

*0.5-microgm. oral dose.
†2.0-microgm. oral dose.

DISCUSSION

Most writers define pernicious anemia in terms of a specific etiologic mechanism: the absence of a substance secreted by the stomach that is essential for intestinal absorption of vitamin B_{12}. Castle,[13] however, does not include the lack of intrinsic (gastric) factor in his definition of pernicious anemia: "Today . . . it can be stated with assurance that pernicious anemia is usually an example of a highly specific isolation of the affected person from his alimentary environment." We use the term "pernicious anemia" in this broader sense so as not to exclude a priori the possibility that pernicious anemia results from a lack of extrinsic (food) factor. Since atrophy of the gastric mucosa of the fundus was a prominent feature of Addison's[14] original description of this disease, the term "Addisonian pernicious anemia" should probably be used to refer exclusively to pernicious anemia occurring as a result of intrinsic-factor deficiency.

The initial appearance of the blood and bone marrow in the case described were characteristic of severe pernicious anemia or severe folic acid deficiency. The unusually large amounts of folic acid present in the patient's diet, the absence of any significant disturbance of intestinal function and the serum vitamin B_{12} level below the range found in patients with folic acid deficiency all militate against the diagnosis of folic acid deficiency. The initial serum vitamin B_{12} of 70 micromicrogm. per milliliter was in the range found in patients with pernicious anemia (0-85 micromicrogm. per milliliter), and when it occurs in association with a macrocytic anemia this level is considered by Lear et al.[11] to be diagnostic of pernicious anemia. The hematologic response was characteristic of pernicious anemia after vitamin B_{12} therapy. On the basis of these findings, the diagnosis of pernicious anemia, as defined in the discussion presented above, seems clear in this case.

The serum iron level was not determined on admission. Eighteen days after the beginning of therapy the serum iron concentration was normal but sub-

sequently continued to drop until an abnormally low level was reached at a time when the red-cell count rose to its maximum (Fig. 1). After stabilization of erythropoiesis, as reflected by the constant red-cell count, the serum iron rose during the next two months to a normal level. These changes in the serum iron concentration are in general agreement with those described by Moore, Doan and Arrowsmith.[15] It is

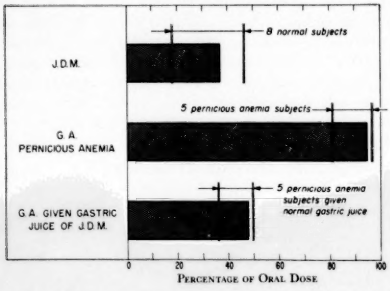


FIGURE 2. *Fecal Elimination of Cobalt*^{60}*-Labeled Vitamin* B_{12} *Measured in a Ten-Day Stool Collection after the Ingestion of 0.5 Microgm.*

of interest that the initial rise in the latent iron-binding capacity of 125 microgm. per 100 ml. is greater than the initial fall in serum iron of 88 microgm. per 100 ml. This disproportionate increase in latent iron-binding capacity is characteristic of the iron-deficiency state.[16] From changes in total body hemoglobin and the mean erythrocyte life span it was calculated that during the period of maximal erythropoiesis approximately 42 mg. of iron per day was required by the bone marrow for hemoglobin formation as compared with this patient's initial equilibrium requirement of approximately 4.5 mg. per day. Since the total plasma volume on the eighteenth hospital day contained approximately 1.8 mg. of iron, it is apparent that a greatly increased rate of transfer of iron from body stores to plasma occurred during the period of increased erythropoiesis. This transfer may have been facilitated by the low plasma iron resulting from accelerated removal of plasma iron to the marrow for increased erythropoiesis. Later, as the rate of removal of iron from the plasma by the bone marrow decreased, entry of iron into the plasma from body stores exceeded the exit of iron from the plasma to the bone marrow, and the plasma iron level rose to the normal range.

Unequivocal proof of normal vitamin B_{12} absorption in this case could have been obtained if the hematologic response to therapy had resulted from the daily oral administration of nothing other than 5 microgm. of vitamin B_{12}, for it has repeatedly been demonstrated that patients with intrinsic-factor deficiency will not have an optimal hematologic response to such an oral dose. Because of the patient's critical condition on entry, it was not feasible to attempt such limited oral vitamin B_{12} therapy and the omission of folic acid and other vitamins from the initial treatment. The investigation of vitamin B_{12} absorption had to be undertaken by means other than the classic reticulocyte response. After the oral administration of cobalt^{60}-labeled vitamin B_{12}, the fecal elimination and urinary excretion, and the hepatic deposition of cobalt^{60} were measured and found to be normal. Normal intrinsic-factor potency was additionally demonstrated by the capacity of the patient's gastric juice to produce normal vitamin B_{12} absorption in a subject with pernicious anemia.

Since absorption of vitamin B_{12} was normal in this patient with pernicious anemia, one may conclude that if significant bacterial synthesis of vitamin B_{12} occurred,[17] it did not take place at a sufficiently high level to be absorbed from the intestinal tract.

Pernicious anemia resulting from a lack of vitamin B_{12} in the diet must be uncommon, for we know of no similarly documented case. Since malnutrition exists throughout the world in almost every conceivable form, the question arises why this mechanism has not previously been observed. At least four factors contribute to the rarity of this condition. In the first place only 10 to 15 per cent of the average dietary amount of vitamin B_{12} is needed to prevent the de-

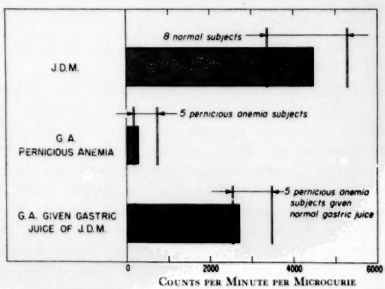


FIGURE 3. *Hepatic Deposition of Cobalt*^{60} *Measured at the Skin Surface over the Liver Ten Days after the Ingestion of 0.5 Microgm. of Cobalt*^{60}*-Labeled Vitamin* B_{12}.

velopment of pernicious anemia; to obtain a vitamin B_{12} intake significantly below this preventive level, the diet must exclude virtually all meat, fish, fowl, dairy products and unrefined grain with its products. Secondly, these drastic dietary deficiencies must exist without simultaneously evoking other severe nutritional deficiencies or starvation. It is well established that specific diseases due to dietary deficiencies occur only when these deficiencies are severe relative to the supply of other substances in the diet. Beriberi, pellagra and scurvy do not occur as the result of pure starvation. Thirdly, even if these first two conditions were met completely, they would have to be satisfied continuously for at least two years. Mac-

Donald, Ingelfinger and Belding[18] reported that of 11 patients not receiving liver therapy in whom pernicious anemia followed total gastrectomy, in 9 the anemia appeared four years or more after surgery. Fourthly, the recent widespread oral and parenteral use of antianemic and multivitamin preparations that include folic acid or vitamin B_{12} makes it improbable that a patient who became symptomatic by satisfying the three conditions mentioned above would not receive ameliorative "shotgun" therapy before hospitalization. In the many areas of the world where these vitamin preparations are not available, the diagnostic facilities for establishing the diagnosis of pernicious anemia due to lack of extrinsic factor are also not available.

The difficulty of simultaneously fulfilling all four requirements mentioned above seems a plausible explanation of the rarity of pernicious anemia due to a dietary lack of vitamin B_{12}. This study, then, does not elucidate an etiologic mechanism that is applicable to a considerable proportion of cases of pernicious anemia. The observations presented surely should not be used to justify the indiscriminate oral administration of vitamin B_{12} to patients in whom the diagnosis of pernicious anemia is suspected or established.

Castle's observations led to the hypothesis that a deficiency of either food factor or the gastric factor could result in the development of pernicious anemia. This study further substantiates the hypothesis by demonstrating that, in this case, a markedly prolonged, drastic deficiency of food factor (vitamin B_{12}) resulted in the development of severe pernicious anemia.

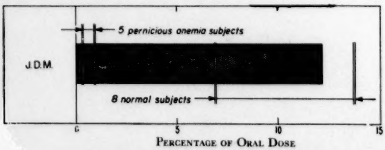


FIGURE 4. *Urinary Excretion of Cobalt^{60}-Labeled Vitamin B_{12} Measured in a Twenty-four-Hour Collection of Urine after the Ingestion of 2.0 Microgm., with Simultaneous Subcutaneous Injection of 1000 Microgm. of Nonlabeled Vitamin B_{12}.*

Summary and Conclusions

A case of pernicious anemia due to dietary lack of vitamin B_{12} resulting from complete refusal to ingest any food of animal origin for more than eight years was studied in detail, and the findings are presented. To our knowledge, this is the first time that such a cause of pernicious anemia has been established. The diagnosis was made on the basis of characteristic morphologic changes of the blood and bone marrow, a serum vitamin B_{12} level in the pernicious-anemia range and a characteristic hematologic response to therapy.

A marked fall in serum iron after vitamin B_{12} therapy and a subsequent rise were observed. These changes were related to variations in the rate at which iron was utilized by the bone marrow for erythropoiesis.

Vitamin B_{12} absorption, as determined by fecal elimination and urinary excretion of cobalt^{60}-labeled vitamin B_{12} and hepatic deposition of cobalt^{60}, was shown to be normal. In addition, the potency of the intrinsic factor of the patient's gastric juice was found to be normal as determined by its capacity to produce normal vitamin B_{12} absorption in a patient with pernicious anemia in remission when it was ingested simultaneously with radioactive vitamin B_{12}.

The exceptional conditions that must be satisfied simultaneously for the development of pernicious anemia due solely to dietary deficiency of vitamin B_{12} are discussed and offered in explanation of the rarity of this mode of pathogenesis. The chief significance of this study lies in its further substantiation of Castle's hypothesis by demonstrating that an extremely prolonged, virtually complete dietary deficiency of vitamin B_{12} can result in the development of severe pernicious anemia.

We are indebted to Dr. Maurice B. Strauss for his encouragement and helpful suggestions in the preparation of the manuscript.

References

1. Berk, L., et al. Observations on etiologic relationship of achylia gastrica to pernicious anemia. X. Activity of vitamin B_{12} as food (extrinsic) factor. *New Eng. J. Med.* **239**:911-913, 1948.
2. Castle, W. B. Observations on etiologic relationship of achylia gastrica to pernicious anemia. I. Effect of administration to patients with pernicious anemia of contents of normal human stomach recovered after ingestion of beef muscle. *Am. J. M. Sc.* **178**:748-763, 1929.
3. Lewis, U. J., Register, U. D., Thompson, H. T., and Elvehjem, C. A. Distribution of vitamin B_{12} in natural materials. *Proc. Soc. Exper. Biol. & Med.* **72**:479-482, 1949.
4. Bowes, A. de P., and Church, C. F. *Food Values of Portions Commonly Used*. 58 pp. Philadelphia: Bowes, 1946.
5. Hall, B. E., and Campbell, D. C. Vitamin B_{12} therapy in pernicious anemia. I. Effect on hematopoietic system: preliminary report. *Proc. Staff Meet., Mayo Clin.* **23**:584-590, 1948.
6. Bethell, F. H., Meyers, M. C., and Neligh, R. B. Vitamin B_{12} in pernicious anemia and puerperal macrocytic anemia. *J. Lab. & Clin. Med.* **33**:1477, 1948.
7. Riddle, M. C. Pernicious anemia: erythrocyte response to treatment. *Am. J. M. Sc.* **200**:145-154, 1940.
8. Kitzes, G., Elvehjem, C. A., and Schuette, H. A. Determination of blood plasma iron. *J. Biol. Chem.* **155**:653-660, 1944.
9. Rath, C. E., and Finch, C. A. Chemical, clinical, and immunological studies on products of human plasma fractionation. XXXVIII. Plasma iron transport: measurement of iron binding capacity of serum in man. *J. Clin. Investigation* **28**:79-85, 1949.
10. Mollin, D. L., and Ross, G. I. M. Vitamin B_{12} concentrations of serum and urine of normals and of patients with megaloblastic anaemias and other diseases. *J. Clin. Path.* **5**:129-139, 1952.
11. Lear, A. A., Harris, J. W., Castle, W. B., and Fleming, E. M. Serum vitamin B_{12} concentration in pernicious anemia. *J. Lab. & Clin. Med.* **44**:715-722, 1954.
12. Pollycove, M., and Apt, L. Absorption, elimination, and excretion of orally administered vitamin B_{12} in normal subjects and in patients with pernicious anemia. *New Eng. J. Med.* (in press).
13. Castle, W. B. Development of knowledge concerning gastric intrinsic factor and its relation to pernicious anemia. *New Eng. J. Med.* **249**:603-615, 1953.
14. Addison, T. *A Collection of the Public Writings of Thomas Addison*. Edited by Dr. Wilks and Dr. Daldy. 239 pp. London: New Sydenham Society, 1868. P. 211.
15. Moore, C. V., Dinan, C. A., and Arrowsmith, W. R. Studies in iron transportation and metabolism. II. Mechanisms of iron transportation: its significance in iron utilization in anemic states of varied etiology. *J. Clin. Investigation* **16**:627-648, 1937.
16. Pollycove, M., Apt, L., and Ross, J. F. Unpublished data.
17. Girdwood, R. H. Intestinal content in pernicious anemia of factors for growth of *Streptococcus faecalis* and *Lactobacillus leichmannii*. *Blood* **5**:1009-1016, 1950.
18. MacDonald, R. M., Ingelfinger, F. J., and Belding, H. W. Late effects of total gastrectomy in man. *New Eng. J. Med.* **237**:887-896, 1947.

IDIOPATHIC BENIGN HYPERGLOBULINEMIC PURPURA*

GEORGE E. SEIDEN, M.D.,† AND HAROLD A. WURZEL, M.D.‡

PHILADELPHIA

THE term, hyperglobulinemic purpura, was used by Waldenström[1,2] in 1943 to describe a syndrome consisting of benign recurrent nonthrombocytopenic purpura, high sedimentation rate and unexplained increase in serum gamma globulin. By the end of 1953, 13 cases had been reported, 12 from Europe and 1 from the United States. These cases were summarized recently by Taylor and Battle.[3] Since 1953 occasional new cases have been presented by authors in Europe.[4,5] This report describes what appears to be the second case of hyperglobulinemic purpura in the United States.

CASE REPORT

Mrs. B. L. was first seen by us in June, 1955, at the age of 29. She had first noted a purpuric rash distributed over the lower extremities in 1951 during the last trimester of her 1st pregnancy. The rash persisted for 2 days and was unaccompanied by other symptoms. From this time she remained well until 1954, when, during the last trimester of her 2d pregnancy, purpura of the legs and thighs recurred and persisted for several weeks. After a normal full-term delivery she remained well until 4 months later, when purpura recurred for the 3d time. It was now widespread over the lower extremities, and made worse by long hours of standing on her feet. Showers of purpuric spots occurred intermittently during the remainder of 1955. The purpuric spots occurred predominantly on the legs and thighs, but on some occasions were found on the buttocks and lower abdomen, and once on the left wrist. The rash was associated at times with tenderness of the leg muscles and swelling of the feet and ankles. However, there were no accompanying constitutional signs of illness, so that she has been able to continue a heavy schedule of work as a graduate nurse. The only residual abnormality as of January, 1956, after numerous episodes of purpura throughout 1955, consisted of scattered brown spots distributed over the lower extremities (Fig. 1).

The past history revealed measles, whooping cough and tonsillitis during childhood years. A tonsillectomy had been performed in 1945, and appendectomy and oöphorectomy on the left in 1948. In 1949 the patient had left-sided cervical adenitis, biopsy of which showed nonspecific lymphadenitis. The menstrual periods had started at the age of 14 and had been regular, of moderate flow and usually of 6 days' duration. She had never exhibited abnormal bleeding tendency, nor was there a familial bleeding diathesis. She had taken no medicine or drugs before the onset of her illness. She used Revlon face powder, Lux or Camay soap, and Arrid deodorant. She had no household pets. In May, 1955, a therapeutic trial of prednisone (Meticorten), 40 mg. daily for 1 month, was without effect on either purpura or associated muscle soreness. For 2 months she kept a careful food diary but was unable to discover a food related to the onset of purpura.

Physical examination in June, 1955, showed a well nourished woman who was 173 cm. (68 inches) tall and weighed 51.3 kg. (113 pounds). There was a diffuse purpuric rash on both lower extremities. The ankles were not edematous; there was no muscle tenderness, and foot pulses were palpable bilaterally. There were several discrete, soft cervical and axillary lymph nodes. The right kidney was palpable, and there was a right-lower-quadrant scar. The remainder of the examination, including ophthalmoscopic examination, was negative.

The temperature was 98.2°F., the pulse 68, and the respirations 18. The blood pressure was 92/60.

Examination of the blood showed a hemoglobin of 10.3 gm. per 100 ml. and a white-cell count of 5900, with a normal differential. Platelet counts on 2 occasions were 262,000 and 336,000. The clotting time was 20 minutes (within normal limits). The serum prothrombin time was 44.8 seconds (normal value, at least 27 seconds) at the end of 1 hour. Clot retraction was good. One-stage prothrombin and accelerator-globulin tests revealed values of 100 per cent. Heparin titration was 0.18 (within normal limits). A peripheral-blood smear showed mild hypochromia. The tourniquet test was negative, as was bone-marrow examination. Cryoglobulins were not found in the serum. The sedimentation rate (Wintrobe method) was 45 mm. per hour (corrected) in June, 1955, and 49 mm. per hour in January, 1956. L.E.-cell preparations were negative in March and July, 1955, and January, 1956. The serum protein was 8.7

FIGURE 1. *Photograph of the Legs of Mrs. B. L. Taken during a Period of Remissions between Episodes of Acute Purpura.*

The spots of brownish discoloration due to previous purpura can be seen.

*From the Diagnostic Clinic and Hospital, University of Pennsylvania.

†Associate in medicine, University of Pennsylvania School of Medicine.

‡Instructor in medicine, University of Pennsylvania School of Medicine; associate, William Pepper Laboratory, University of Pennsylvania Hospital.

gm. per 100 ml., of which 3.6 gm. was albumin and 5.1 gm. globulin. Electrophoretic analysis of serum protein in June, 1955, revealed an albumin of 4.12 gm., alpha-1 globulin of 0.25 gm., alpha-2 globulin of 0.80 gm., beta globulin of 1.0 gm. and gamma globulin of 2.73 gm. per 100 ml. A repeat determination in January, 1956, showed an albumin of 3.1 gm., alpha-1 globulin of 0.39 gm., alpha-2 globulin of 0.61 gm., beta globulin of 0.98 gm. and gamma globulin of 3.21 gm. per 100 ml. The gamma-globulin value was higher than normal for both determinations (normal range for females, 0.72 to 1.51 gm. per 100 ml.). The gamma peak was broad and dome shaped. Ultracentrifugation of the serum protein revealed the following:

M component: 4 per cent sedimented as S_{20}^{0} = 13.4S
G component: 21 per cent sedimented as S_{20}^{0} = 5.1S
A component: 75 per cent sedimented as S_{20}^{0} = 3.1S.

This analysis demonstrated no increase in the high-molecular-weight fraction.

An x-ray film of the chest and an electrocardiogram were normal. Urinalysis was negative. The blood urea nitrogen

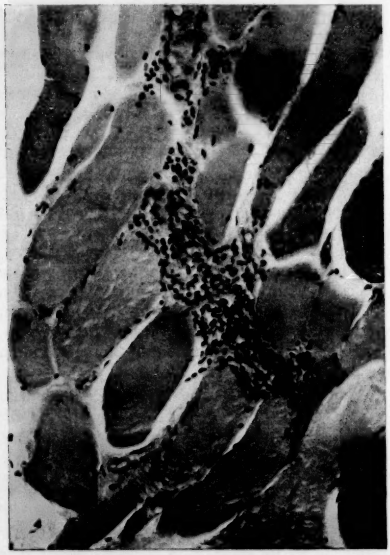


FIGURE 2. *Photomicrograph of a Biopsy Specimen of Calf Muscle, Showing Perivasculitis.*

was 8 mg. per 100 ml. Muscle biopsy performed in March, 1955, during the time of active purpura and muscle soreness, revealed nonspecific perivasculitis (Fig. 2). The vasculitis involved small vessels and was not characteristic of lupus erythematosus or periarteritis nodosa. The electrophoretic pattern of the serum protein is shown in Figure 3.

DISCUSSION

This patient exhibited most of the features of hyperglobulinemic purpura outlined by Waldenström[2] and noted in the 13 cases reviewed by Taylor and Battle.[3] These features are listed in Table 1.

To establish a diagnosis of idiopathic hyperglobulinemic purpura, it is necessary to rule out the presence of underlying systemic disease that may be associated with elevated gamma globulin and purpura. Purpura with hyperglobulinemia has been noted in association with lupus erythematosus, sarcoidosis, multiple myeloma and Sjögren's syndrome.[2] Although patients with hyperglobulinemic purpura have remained well for as long as nineteen years (over half the patients

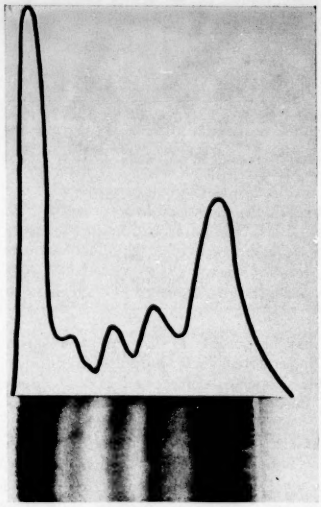


FIGURE 3. *Electrophoretic Pattern of the Serum Protein. Reading from left to right, the peaks correspond to albumin, 3.1 gm., alpha globulin, 0.39 gm., alpha-2 globulin, 0.61 gm., beta globulin, 0.98 gm., and globulin, 3.21 gm.*

in the reported cases have been well for at least ten years and the patient described above was constitutionally well for five years, it is not possible to exclude entirely the possibility of future development of underlying systemic disease. Studies in the case reported above, including history and physical examination, muscle biopsy, bone-marrow examination, L.E.-cell preparations, blood counts, urinalysis, electrocardiogram and x-ray study of the chest, gave no evidence of systemic diseases known to be associated with hyperglobulinemia and purpura.

In addition to the exclusion of underlying systemic illness, the diagnosis of idiopathic hyperglobulinemic purpura depends on exclusion of other hemorrhagic diatheses associated with cryoglobulinemia or macroglobulinemia. Cryoglobulinemic purpura is made worse by cold, and is frequently associated with Raynaud's phenomenon. Cryoglobulins can be demonstrated in the blood. In none of the cases of hyperglobulinemic purpura were these features demonstrable, nor were they present in the case reported

above. Macroglobulinemic purpura[2-4] or purpura associated with large globulin molecules in the blood must also be included in the differential diagnosis. Macroglobulinemic purpura usually occurs in elderly men with osteoporosis and generalized bleeding; some of these patients have had associated multiple myeloma. Macroglobulinemic purpura was positively excluded, in the case presented above, by ultracentrifuge studies of the serum protein, which revealed no increase in high-molecular-weight protein molecules.

Table 1. *Features of Hyperglobulinemic Purpura.*

Subject of Analysis	Sex	Duration	Coagulation Defects	Cryoglobulins	Sedimentation Rate	Gamma Globulin	Electrophoretic Pattern	Anemia	Purpuric Lesions
Present case	Female	Good health after 5 yr.	None	None	Elevated	Slight to moderate increase	Broad gamma-globulin peak	Present	Recurrent bouts; predominantly on lower extremities.
13 cases summarized by Taylor & Battle[3]	75% females	55% well after 10 yr.; remainder well as of last report except 1 dead from unrelated causes.	None	None	Elevated in all but 1 case	Slight to moderate increase (marked increase in 1 case)	Broad gamma-globulin peak except in 1 case	Present in all but 1 case	Recurrent bouts; predominantly on lower extremities.

It may be possible to differentiate idiopathic benign hyperglobulinemic purpura from other nonthrombocytopenic purpuras such as drug-induced purpura, purpura annularis telangiectodes (Majocchi's disease) and Henoch's and Schönlein's purpura, if preliminary observations[6] that the gamma-globulin fraction is normal in these conditions are confirmed.

The etiology and pathogenesis of benign hyperglobulinemic purpura are obscure. The occurrence of purpura without coagulation defect in association with a variety of serum-protein disturbances is intriguing. The biopsy specimen obtained in this case may throw some light on the pathogenesis of this syndrome. The vasculitis seen in Figure 2 may result in capillary-membrane impairment and hence bleeding. The monocytoid-cell perivascular infiltration is not characteristic of periarteritis nodosa or lupus erythematosus and must be classified as nonspecific. The pathologic changes may represent a hyperergic response, of which the disturbed gamma globulin may be another manifestation.

It is of interest that similar pathologic changes were observed in a skin-biopsy specimen from a patient with idiopathic benign hyperglobulinemic purpura reported by Kay and Robertson[7] in England. They noted cuffs of inflammatory cells surrounding small blood vessels in their case. We have not been able to find any further descriptions of pathological specimens from patients with this illness.

In conclusion, if there is such a syndrome as benign hyperglobulinemic purpura, — that is, if the patients with known cases continue to enjoy good health despite purpura, — the case presented above seems to fit that classification and to represent the second reported American case.

Summary

The second case of benign hyperglobulinemic purpura reported in the United States is presented. The patient was a young woman who exhibited recurrent purpura confined largely to the lower extremities and associated with rapid sedimentation rate and increased gamma globulin, but with no other demonstrable evidence of systemic disease. Muscle biopsy showed nonspecific perivasculitis. The patient has remained well for five years.

We are indebted to Dr. Sam Sorof, of the Institute for Cancer Research, Fox Chase, Philadelphia, for performing the ultracentrifuge analysis.

References

1. Waldenström, J. Clinical methods for determination of hyperproteinemia and their practical value for diagnosis. *Nord. med.* **20**:2288-2295, 1943.
2. *Idem.* Abnormal proteins in myeloma. *Advances Int. Med.* **5**:398-440, 1940.
3. Taylor, F. E., and Battle, J. D., Jr. Benign hyperglobulinemic purpura: case report. *Ann. Int. Med.* **40**:350-356, 1954.
4. Fallet, G. H., and Haenni, A. A propos d'un nouveau cas de purpura hyperglobulinémique de Waldenstroem. *Praxis* **43**:71-76, 1954.
5. Vannucchi, V., and Doni, A. A proposito di un caso di porpora iperglobulinemica. *Riv. crit. di clin. med.* **54**:4, 1954.
6. Bernfeld, P., and Stefanini, M. Characteristic electrophoretic patterns in hemophilia and idiopathic thrombocytopenia. *Proc. Soc. Exper. Biol. & Med.* **77**:551-553, 1951.
7. Kay, H. E. M., and Robertson, K. M. Benign hyperglobulinaemic purpura. *J. Path. & Bact.* **70**:543, 1955.

MEDICAL PROGRESS

DIABETES MELLITUS

SAMUEL B. BEASER, M.D.*

BOSTON

IN this report the following aspects of diabetes mellitus are considered: biochemistry and physiology; insulin and its metabolism; endocrine effects; pathology and pathogenesis; diagnosis; clinical diabetes; therapy, insulin and hypoglycemic sulfonamides; pregnancy and diabetes; and complications.

CARBOHYDRATE METABOLISM

Experimental diabetes has continued to shed light on the biochemical defects of human diabetes. Several sites have been suggested for these defects.† It is not always easy to distinguish between the various possibilities and to decide which defects are primary and which secondary effects of the diabetic state.

In a previous review,[3] evidence for a diabetic defect in transfer of glucose across the cell membrane was given. Several methods have since been used to ascertain that the experiments truly measured this process of transfer rather than intracellular metabolic processes beyond it. In the first place the glucohexokinase reaction and glucose oxidation were inhibited by low temperature[4] or by competitive metabolites[5,6] (glucosamine, betahydroxybutyric acid), and yet the transfer defect was still demonstrable. Another method used to distinguish between the two processes was to measure the free glucose versus glucose-6-phosphate in tissues of diabetic rats after injection of tagged glucose.[7] Still another was to study the tissue sequence of utilization and oxidation in the eviscerated rabbit.[6] In all these experiments, a transfer defect was distinguishable.

The second defect, that of hexokinase phosphorylation, has not been demonstrable in homogenates, even that of human diabetic muscle.[8] In diabetic liver slices, however, glucose utilization was found to be reduced to a fourth to a tenth of the normal value as compared with fructose, which is assumed not to require glucohexokinase.[9]‡ A new diabetic defect in this area has been demonstrated — namely, a twofold increase in glucose-6-phosphatase activity.[10] This enzyme reconverts the active glucose-6-phosphate to inactive glucose, so that an increase could be potentially important.

A diabetic defect in the concentration of carriers of high-energy phosphate (that is, adenosine triphosphate) could not be demonstrated in so sensitive a preparation as rat diaphragm.[11]

Beyond this point, glucose is utilized traditionally by the glycolytic Embden–Meyerhof pathway. Recently, an alternative oxidative process involving pentose formation has been proposed.[12] Although the necessary enzymes are present in mammalian tissues,[13] it is less readily demonstrated in vivo than in isolated tissues.[14,15] The degree of utilization of this pathway is different in various tissues and is dependent on experimental conditions.[16] Interpretation of results is difficult,[17] but it is believed that there is some increased use of this pathway in fasting and in diabetes.[18]

Evidence has accumulated for diabetic disturbances at the level of the Krebs cycle. In diabetic rats, a phosphorylation defect is reflected in a decreased ability of the liver to transform labeled acetate to citrate.[19] In diabetic liver slices, a greater proportion of pyruvate is directed to glucose than normal,[20] and this is correctible by insulin.[21] The common meeting point of carbohydrate and fat metabolism is at the condensation of oxalacetate and acetyl-coenzyme A.[22] The ketonuria produced when oil is fed to rats can be reduced by feeding of certain Krebs-cycle associates of oxalacetic acid such as succinic and malic acid. This reduction fails to occur in the alloxan-diabetic rat and is corrected by insulin.

The basic action in the Krebs cycle, oxidative phosphorylation, has been localized anatomically to the mitochondria. In hepatic mitochondria of the depancreatized cat, oxidative phosphorylation is impaired so far as adenosinetriphosphate formation is concerned.[2] The actual site of insulin action in this area has been suggested as the important metabolic crossroad of the three major metabolites, the condensation of acetyl-coenzyme A with oxalacetate.

The study of the metabolism of a single organ in vivo, the heart, was performed by the technic of coronary-sinus catheterization in human diabetes and the alloxan diabetes of the dog.[23] The utilization of glucose, pyruvate, lactate and amino acids was diminished, and that of ketones increased. Simultaneously, the important alternate fuel, fat, was extracted from the blood and stored more abundantly by the diabetic myocardium.

The study of the carbohydrate metabolism of single organs in diabetes does not determine which defects

*Clinical associate in medicine, Harvard Medical School; head, Abraham Rudy Diabetes Clinic of the Medical Service, Beth Israel Hospital.

†Recent reviews of value in this field are those by Stetten and Topper[1] and Stadie.[2]

‡It is of interest, in detail, that the proportion of fructose converted to glycogen was considerably reduced as compared with the proportion oxidized.

and organs are of primary and which of secondary importance. Renold et al.[24] have attempted to answer this by studying the time sequence of the correction of deficiencies in the diaphragm muscle and the liver of the alloxan-diabetic rat after insulin administration. The organs were removed for study at varying intervals up to forty-eight hours after insulin had been given. In muscle, only glycogen synthesis from labeled glucose was studied. In liver, the metabolism of labeled glucose, fructose, pyruvate and acetate was followed in greater detail. The basic deficiencies had been established previously.[9] Insulin re-established muscle glycogenesis within ten minutes. By contrast, the repair of hepatic effects was delayed and piecemeal. No effect was apparent in one hour; there was some correction of phosphorylation in twelve to twenty-four hours, and of lipogenesis and gluconeogenesis in twenty-four to forty-eight hours. This suggests that the effect of insulin on muscle is primary, and the hepatic effect secondary. It confirms the delay previously noted in hepatic lipogenesis alone by Chernick and Chaikoff[25] and suggests that the mechanism involves enzyme adaptation. This is also suggested by studies of the oral glucose tolerance test in normal rats after diets of glucose and fructose respectively for three days before the tests.[26] The glucose tolerance was impaired by the fructose. When metabolic studies were performed on individual organs, only the liver was found to be disturbed in this slow three-day process.

The mechanism of conversion of C^{14}-labeled fructose and sorbitol to glycogen in liver and muscle has been studied in the rat in vivo.[27] Whereas the glucose molecule is incorporated intact into liver glycogen, sorbitol is first transformed into hepatic fructose, which is split into two molecules of dihydroxyacetone phosphate before its glycogenesis. By contrast, any fed sorbitol or fructose that appears as muscle glycogen does so after prior conversion to liver glucose.

Fructose utilization requires an intact liver, for it is not utilized in the eviscerated animal (rabbit).[28] It does not penetrate the peripheral cells, or compete with glucose metabolically there.

In alloxan-diabetic rats, orally administered fructose had greater protein-sparing action than glucose.[29] Comparison of its usefulness as a substitute for glucose in diabetic rats showed that the initial advantage in decreasing glycosuria and polyuria became less significant when the experiments were extended up to six or more weeks.[29,30] Yet fructose comprised only 5 per cent of the excreted carbohydrate in these animals, and glucose the rest. In human diabetic patients, in shorter experiments, fructose feeding was compared with glucose feeding after insulin withdrawal. There were beneficial effects on blood sugar and acetone only in the mild or moderately severe, but not in the severe cases.[31] The fate of injected fructose was studied by hepatic venous catheterization in the normal human subject.[32] The splanchnic circulation removed almost half, and of this 20 to 50 per cent was converted to lactic and pyruvic acid.

Tolerance to orally administered glucose in human beings decreases with age, but fructose does not.[33] Thus, the glucose metabolic defect in the aged resembles that of true diabetes.

Inositol excretion has been noted to be increased in diabetes. But, unlike fructose or glucose, it is due to increased renal excretion, not metabolism.[34] This is probably due to competition with glucose in the mechanism of tubular reabsorption.

Fat and Protein Metabolism

The dependence of normal lipogenesis on normal carbohydrate metabolism has been re-emphasized. Coenzyme A is the common link between the two, participating in fatty acid metabolism in its acetyl or acetoacetyl form.[35] The metabolic activities of both liver and adipose tissue have been compared in vitro.[36] The oxidation and lipogenesis of labeled glucose was found to be markedly depressed in diabetic as compared with normal tissues. When insulin was administered to the intact animal, only the rate of lipogenesis was corrected. There was a delay of two and a half days in reverting to normal, reminiscent of the restoration of hepatic carbohydrate metabolism.[24] Moreover, of the two organs, adipose tissue is the site of much more intense activity, truly characterizing it as an organ. Fasting likewise decreased hepatic lipogenesis, when measured after the injection of C^{14}-labeled acetate into the normal adult rat.[37]

Other work has clarified the mechanism involved in the defect. Shaw and Gurin[38] measured lipogenesis in aqueous (particle-free) liver extracts from diabetic rats and pigeons. The virtual absence of synthesis of fatty acids was wholly or in part restored by addition of phosphorylated intermediates of glycolysis but not glucose. The bottleneck may be in glycerol synthesis, as revealed by in vitro studies of utilization of acetate and glucose by lactating mammary gland.[39] This process was stimulated by insulin and acetate, but glycerol could be substituted for the insulin with the same results.

The rate of oxidation of fatty acids has been shown to be independent of glucose concentration in a wide variety of tissue slices and homogenates.[40] This minimizes the usefulness of hyperglycemia in diabetes and reveals an independent basal fat metabolism even in tissues known traditionally to be carbohydrate users.

The rate of incorporation of labeled acetate into cholesterol in diabetic liver slices had been reported to be twice the normal rate.[41] However, measurement of the total cholesterol concentration in the liver of the intact animal has shown no corresponding increase.[42]

The pathway of conversion of long-chain fatty acids to carbohydrate has been worked out in the diabetic dog.[43] The injected palmitic acid was labeled

at the C_1 and C_6 positions. The sequence is degradation to 2-carbon fragments by beta oxidation, conversion to 3-carbon units, presumably by way of the Krebs cycle, and then condensation to glucose by the Embden–Meyerhof pathway. Carotene is converted to vitamin A in the intestinal wall.[44] In alloxan diabetes this is reduced by 75 per cent and accounts for diabetic carotinemia.

In the previous review,[3] the relatively independent role of insulin in promoting growth was elaborated upon. In the hypophysectomized rat, insulin treatment caused a marked increase in the amount and percentage of nitrogen retained, the latter showing an approximately linear relation to the amount of insulin administered.[45]

Insulin and Its Metabolism

The chemical nature of insulin has been considerably clarified. Its basic molecular weight is approximately 5700, with the empirical formula of C254 H377 O75 N65 S6.[46] It is composed of a total of 48 amino acids of 17 different varieties, with approximately 1 to 6 of each type of amino acid per molecule. Structurally, it is composed of two straight chains containing 21 and 30 amino acid units each. Analysis shows specific variation in the distribution and position of the amino acids in insulin from various species. Details of possible structural form have been worked out by physicochemical means and correspond to chemical analysis.[47]

The human diabetic state so obviously resembles experimental hypoinsulinism that a study of the insulin economy in mammals has been vitally needed. The original work of Mirsky on insulin degradation has now been greatly expanded by metabolic studies of labeled (I^{131} and S^{35}) insulin.[48-51] After injection a peak concentration is reached in five to fifteen minutes largely in three organs, — liver, kidney and muscle, — with virtually none in brain. The insulin is bound to liver cells (although not to the cell wall) and cannot be washed out by perfusion as labeled thyroxine can.[52] After twenty-four hours, only 1 or 2 per cent is present in urine as undegraded insulin,[50,51] but fully 50 per cent as degraded metabolic products.[50] In the kidney the labeled product is located in the tubules.

Degradation of insulin occurs largely in the liver and kidney,[48] and the active system in the liver is present after extraction mainly in the supernatant fluid,[53-55] and not in the mitochondria[53] or microsomes.[54] It is only relatively specific for insulin,[50] and can degrade other substances, such as alpha-ACTH, casein, glucagon and growth hormone.[56] Therefore, for the present, the term insulinase is not strictly correct. There are actually two systems: a heat stable one, which reduces the desulfide bonds,[57] and a heat labile one, which acts by proteolysis.[58] The latter is the more active.

Degradation is affected by a variety of conditions. It is decreased by hypophysectomy[58] or thyroidectomy,[59] and increased in thyrotoxicosis.[59] This corresponds to the insulin sensitivity in these clinical states. Nephrectomy diminishes the rate of degradation.*

The naturally occurring inhibitor of this insulin-degrading system is a peptide or polypeptide, which acts by a first-order reaction when injected subcutaneously or intravenously.[60,61] Its mode of action may be as a competitor to insulin in the enzyme system outlined above. Mirsky[61] has suggested the possibility that human diabetes is due to underactivity of this inhibitor. The unavailability of human liver samples from diabetic patients has so far made it impossible to confirm this. But a specific strain of mice has been described with increased insulin tolerance due to an increased insulin-inactivating capacity of the liver.[62] Recently, Mirsky et al.[63] demonstrated a decrease in liver insulinase activity in vivo and in vitro after administration of the hypoglycemic sulfonamides. The action is by noncompetitive inhibition, but the magnitude of the concentrations used in vitro suggests a chemical rather than a pharmacologic effect. They attribute part of the action of these drugs to this mechanism.

Biologic assay of blood insulin concentration indicates not only an elevation after glucose administration but also a measurable basal secretion during fasting.[64] Discrepancies between different methods of assay can be explained, and they illustrate the complexity of the technics. Acromegalic blood, for example, shows less blood insulin than normal by the method of the whole, insulin-sensitive rat and greater than normal by the in vitro rat diaphragm.[65] The former is probably an indirect effect of stimulation of glucagon discharge by growth hormone present in acromegalic plasma. The latter is the immediate, direct hypoglycemic effect of growth hormone on rat diaphragm.[66] In the latter preparation, the insulin effect could be separated out by acid extraction of the test plasma.[65]

It was appropriate next to look for abnormal catabolism of insulin in diabetes. Forty diabetic patients were given 50 to 100 microcuries of labeled insulin intravenously, and insulin catabolism was compared with 26 human controls.[67] Of the 40 diabetic patients 27 retained between four and five times as much of the labeled insulin in their plasma at the end of an hour as the normal controls. This was independent of the type of diabetes. It was shown that diabetic plasma "bound" insulin, preventing its combination with the tissues. Experiments employing prior addition of unlabeled insulin to the human diabetic plasma suggested that excessive retention by the plasma might be due to lack of "saturation" of the plasma insulin-carrying capacity, rather than actual insulin antagonism.

*This may have some bearing on the amelioration of diabetes with nephropathy.

Endocrine Effects on Carbohydrate Metabolism

Glucagon

Further experimental work supports the concept that glucagon is a hormone, but many details still require clarification. The enhancement of glycogenolysis by glucagon in liver slices resembles that of both ephedrine and epinephrine, with certain differences. The glucagon effect is mathematically additive with ephedrine, but not with epinephrine.[68] In man, glucagon and epinephrine have an additive effect on the peak of blood sugar elevation.[69] The effect of glucagon on rat liver slices is to decrease the conversion of glucose and fructose to fatty acids.[70] This results in an increased rate of ketone formation. This effect is opposite to that of insulin and similar to that of epinephrine.

Evidence regarding the effect of glucagon on peripheral utilization of glucose is conflicting. As measured by arteriovenous glucose difference in man, it has an enhancing effect that is antagonized by epinephrine.[71,72] However, it does not need the pancreas or insulin for this effect (in the dog).[72] It has been claimed that glucagon decreases the conversion of glucose to glycogen in rat diaphragm in vitro[73,74] and in dogs in vivo.[75] The former experiments used excessively high concentrations of glucagon, and have not been confirmed by subsequent reports.[76] Similarly, glucagon diminishes transfer of glucose into the intracellular compartment of the eviscerated rabbit, even though the oxidation rate is unchanged.[77]

The origin of glucagon from the alpha cells seems more certain[78]; none is present in acinar cells.[79] Administration of pituitary growth hormone at first increases and later decreases the number of alpha cells, with degranulation and degeneration.[80] Yet the actual presence of the pituitary gland is not necessary for their integrity. Glucagon is destroyed in the liver, as is insulin.[81]

No important role has yet been demonstrated for glucagon in normal carbohydrate metabolism. Destruction of alpha cells by growth hormone causes no physiologic changes.[80] Diabetes is not increased by pancreatectomy in alloxan or metahypophyseal diabetes.[82] Chronic administration of glucagon has no effect on the glucose tolerance or insulin tolerance tests, or the alpha or beta cells of the rat[83] and, curiously enough, even increases hepatic glycogen in the rabbit and rat.[84] Large amounts of glucagon mixed with insulin do not affect its hypoglycemic action.[85] Even in the process of recovery from hypoglycemia, recent work has shown that mammals can recover from insulin-induced hypoglycemia without the hormones of the pancreas or the adrenal or pituitary gland.[86] This does not preclude a supporting role in this process for glucagon or any of the other hormones involved.

Glucagon probably has no important role in human diabetes. The concentration of glucagon in the pancreas is similar to that of lower animals, and the diabetic pancreas does not contain an increased concentration of glucagon.[87] None appears in normal or diabetic urine. Patients with brittle diabetes are more sensitive to the action of glucagon (as they are to insulin) than those with stable disease.[88]

Other Endocrine Glands

Highly purified preparations of growth hormone of the pituitary gland are now available to clarify previous observations. Both in vitro and in vivo growth hormone can produce both an increase or decrease in carbohydrate utilization. This has been regarded as possibly an experimental artifact. In vitro, by rigidly controlling the experimental condition, Ottaway and Bulbrook[66] have been able to demonstrate clearly both effects in rat diaphragm. Stimulation occurs first and at lower concentrations, but both effects reside in the single substance. Moreover, the supportive role of a functioning adrenal gland is necessary for this effect.

Duplicating the action of the impure products, pure growth hormone has produced insulin resistance[89] and metahypophyseal diabetes[81] in the normal dog and an aggravation of the existing diabetes in the diabetic dog.[90] This latter effect occurs promptly, within twenty-four hours, and the relative resistance of the intact dog as contrasted with the diabetic one is ascribed to the protective effects of an insulin-secreting pancreas.

It is in man particularly that the purification of growth hormone has made possible experiments previously hampered by toxic impurities. After the acute administration of growth hormone to normal human subjects, ketonemia occurred, but no alteration in blood sugar level.[91] In chronic experiments over a period of weeks, a worsening of the glucose tolerance test occurred in some persons,[92] and in diabetic patients more prompt effects on blood sugar but little ketonemia was produced.

Although the end result of growth hormone action may be to increase growth, the sequence of metabolic events gives temporal priority to other processes.[91,93,94] The first effect is the mobilization of fat,[95] followed by increased hepatic lipid catabolism[96] and finally by decreased peripheral carbohydrate utilization.[94] The last usefully conserves three carbon elements for protein anabolism. The insulinogenic action of a functioning pancreas prevents overaction of the inhibition of carbohydrate metabolism. If the pancreatic function deteriorates under the strain, diabetes results.

The diabetogenic effect of hyperactivity of pituitary or adrenal gland is usually reversible in man. A useful comparative study in a variety of species has been made of the effects of these hormones either

alone or combined with partial pancreatectomy.[97] The results showed that species differences are quantitative rather than qualitative. It has been confirmed that cortisone prevents the diabetogenic effect of growth hormone in depancreatized dogs.[98] Its pancreatropic action may be responsible for this effect, as indicated below.

The effects of adrenocortical hormones on carbohydrate metabolism have been further clarified. The acute effect in mice is to decrease glucose utilization to 65 per cent of normal, with oxidation reduced by 50 per cent.[99] In chronic experiments in the guinea pig over-all glucose utilization was found to be apparently unimpaired because the glycosuria was compensated for by an increased food intake and gluconeogenesis.[100] Transient diabetogenic effects were produced in rats by administration of cortisone for a month, mainly owing to peripheral inhibition of glucose utilization.[101] In human beings, after single doses or multiple doses over several days, both ACTH and cortisone decreased oral glucose tolerance and also glucose insulin tolerance.[102,103]

After chronic administration, adrenocortical hormones produce islet-cell hyperplasia and new-cell formation in the guinea pig,[100] the rat[101] and the rabbit.[104] This explains the self-limited nature of the diabetogenic effect (the role of the pituitary gland was discussed in the previous review[3]). It also provides a possible explanation for the reversal of alloxan diabetes of rats by administration of compound E.[105]

The diabetogenic potency of cortisone or hydrocortisone is reduced considerably in the rat if the liver has been removed, whereas the action of adrenocortical extracts is not adversely affected.[106] This suggests that the pure products require biologic activation by the liver, whereas the latter do not.

Thyroid overactivity produces an increased rate of glucose oxidation and utilization.[107] This is demonstrable only by the intravenous glucose tolerance test; the oral test shows the reverse. In human diabetes, newer histologic methods (differential thyroid cell counts) reveal overactivity of the thyroid gland in many patients, but not in the toxic range.[108] Furthermore, pituitary cell counts show that some of these are due to increased pituitary thyrotropic function.

Estrogens have been reported to have an ameliorative effect on diabetes of both the alloxanized and depancreatized rat.[109] As with cortisone, there is a diphasic effect, with histologic evidence of islet-cell hyperplasia to explain the recovery. Others have been unable to confirm this in either the rat[110] or the rabbit.[111]

Changes in gonadal function in diabetes have long been noted clinically. Male sexual function has recently been studied in 64 diabetic patients of all ages.[112] Of 15 of the younger ones with diabetes of recent onset, 60 per cent showed impotence and diminished libido; proper regulation of the diabetes restored normal function in 60 per cent of them. The 17-ketosteroid excretion was found to be decreased in all the patients, but more so in those with poor control and decreased sexual function. The mechanism is probably decreased testicular 17-ketosteroid production, which is due in turn to decreased pituitary gonadotropin activity. The findings in the female diabetic patients were less striking — namely, an earlier menarche and menopause.[113]

Pathology and Pathogenesis of Diabetes Mellitus

In the pathogenesis of human diabetes heredity is still paramount. Because of difficulties in the collection of human data and the tendency for diabetes to appear late, genetic predictions are at best only estimates. Steinberg[114] has attempted such calculation. From the information of the incidence of diabetes in the parents, he could set up predictions of the proportion of the siblings of a diabetic patient who would be observed to be diabetic, and from the information of the incidence of diabetes in grandparents he could predict those who would genetically be likely to become diabetic. Finally, the probability that a nondiabetic person is genetically liable to diabetes is predictable from the known diabetic relatives. For case-finding purposes, those with 50 to 80 per cent liability to diabetes are important to know and consist of those with one diabetic parent and, in addition, either a sibling or a parent (or both) of the nondiabetic parent.

He has calculated that age at onset of diabetes in a diabetic parent or sibling has no causal relation to age at onset of diabetes in a given patient.[114] He showed that previous pregnancy is not significant statistically in initiating or altering the incidence of diabetes in the female sex.[115] And he further showed that diabetes or a tendency to diabetes in the mother at the time of childbirth has no *statistical* significance in predetermining the genesis of diabetes in the children or the age at which it occurs, although he did not rule out the possibility in individual cases.

Although there is agreement on the factor of heredity, there is no clear-cut evidence of what the inherited defect actually is. Although alloxan chemically resembles many naturally occurring metabolic products, so far neither it nor its derivatives have been implicated in the human disease. But its damaging effect on the pancreas must be due to specific toxicity, since studies with injected C^{14}-labeled alloxan-2 in the rat have shown that it does not accumulate specifically in the pancreas.[116]

One possible mechanism suggested for human diabetes has been overproduction of glucagon by the pancreatic alpha cells, as occurs in hereditarily obese and hyperglycemic mice.[117] No increase of glucagon has been found in the human diabetic pancreas.[57]

Another possible mechanism is excessive insulin inactivation. Spontaneous "insulin resistance" of mice utilizes this mechanism, but there is no evidence of this in spontaneous human diabetes.

The oldest theory, hypoinsulinism, continues to be actively investigated. Measurement of the total insulin in the normal human pancreas shows remarkable uniformity, regardless of the variability of its concentration per gram of actual (fat-free) parenchyma.[118]

The occurrence of diabetes with almost complete lack of pancreatic insulin in human beings has been largely confined to youth, and, on this basis, age dependence has been postulated to be due to pituitary influences ("growth type"). This becomes less credible as a result of the finding that the spontaneous diabetes of the dog is solely of this type but occurs only in adult dogs.[119]

There are now three independent methods of evaluating extractable pancreatic insulin. These include extraction and biologic assay, beta-cell granule stain and a more specific sulfhydryl stain. The Wilson–Gomori stain for beta granules can be made microquantitative, correlating well with the biologic-assay method.[120] In human diabetic pancreases, more assayable insulin is present than can be accounted for by the granules, and this is attributed to the probable occurrence of some insulin in smaller aggregates.

Barrnett et al.[121] have developed a relatively specific method for staining the pancreas for sulfhydryl and disulfide-containing protein. This method, unlike stains for beta-cell granules, does stain insulin in vitro. Moreover, although the islet material stained by the method is less granular in appearance than the beta granules, it corresponds quantitatively with the latter and with biologic assays. This is so both in normal subjects and under a variety of experimental conditions known to affect pancreatic insulin content. This was confirmed by studies of six different species.

Barrnett's work has further confirmed the extensive evidence for the very dynamic qualities of islet tissue. Histologic details of spontaneous recovery from alloxan diabetes[121-123] parallel the process of new islet-cell formation that is known to occur under hormonal influences. In both instances, new cells are formed mainly from acinar or ductular epithelium, and less frequently if at all from alpha or other islet cells. This may provide an anatomic background for clinical observations of fluctuations of human diabetes — particularly in youth but in adult life too.[124,125]

(To be concluded)

References

1. Stetten, D., Jr., and Topper, Y. J. Metabolism of carbohydrates: review. *Am. J. Med.* **19**:96-110, 1955.
2. Stadie, W. C. Current views on mechanisms of insulin action. *Am. J. Med.* **19**:257-273, 1955.
3. Beaser, S. B. Diabetes mellitus. *New Eng. J. Med.* **251**:698-705, 1954.
4. Park, C. R., Bornstein, J., and Post, R. L. Effect of insulin on free glucose content of rat diaphragm in vitro. *Am. J. Physiol.* **182**:12-16, 1955.
5. Nakada, H. I., Toshiko, N. M., and Wick, A. N. Studies on relationships between insulin, glucosamine, and glucose in rat diaphragms. *J. Biol. Chem.* **215**:803-808, 1955.
6. Drury, D. R., and Wick, A. N. Mechanism of insulin action. *Diabetes* **4**:203-206, 1955.
7. Park, C. R., and Johnson, L. H. Effect of insulin on transport of glucose and galactose into cells of rat muscle and brain. *Am. J. Physiol.* **182**:17-23, 1955.
8. Auld, W. H. Hexokinase activity of skeletal muscle in diabetes mellitus. *Clin. Sc.* **13**:357-364, 1954.
9. Renold, E., Hastings, A. B., and Nesbitt, F. B. Studies on carbohydrate metabolism in rat liver slices. III. Utilization of glucose and fructose by liver from normal and diabetic animals. *J. Biol. Chem.* **209**:687-696, 1954.
10. Langdon, R. G., and Weakley, D. R. Influence of hormonal factors and of diet upon hepatic glucose-6-phosphatase activity. *J. Biol. Chem.* **214**:167-174, 1955.
11. Ottaway, J. H. Effect of insulin on anaerobic metabolism of rat diaphragm. *Biochem. J.* **61**:441-447, 1955.
12. Weinhouse, S. Newer pathways of carbohydrate metabolism. *Diabetes* **4**:173-177, 1955.
13. Glock, G. E., and McLean, P. Preliminary investigation of hormonal control of hexose monophosphate oxidative pathway. *Biochem. J.* **61**:390-397, 1955.
14. Bloom, B., Eisenberg, F., Jr., and Stetten, D., Jr. Glucose catabolism in liver slices via phosphogluconate oxidation pathway. *J. Biol. Chem.* **215**:461-466, 1955.
15. Bloom, B. Catabolism of glucose by mammalian tissues. *Proc. Soc. Exper. Biol. & Med.* **88**:317, 1955.
16. Katz, J., Abraham, S., Hill, R., and Chaikoff, I. L. Occurrence and mechanism of hexose monophosphate shunt in rat liver slices. *J. Biol. Chem.* **214**:853-868, 1955.
17. Wood, H. G. Significance of alternate pathways in metabolism of glucose. *Physiol. Rev.* **35**:841-859, 1955.
18. Bloom, B. Fraction of glucose catabolized via Embden-Meyerhof pathway: alloxan diabetic and fasted rats. *J. Biol. Chem.* **215**: 467-472, 1955.
19. Frohman, C. E., and Orten, J. M. Tracer studies of acids of tricarboxylic acid cycle. I. Fate of labeled acetate in livers of normal and diabetic rats. *J. Biol. Chem.* **216**:795-799, 1955.
20. Landau, B. R., Hastings, A. B., and Nesbett, F. B. Origin of glucose glycogen carbons formed from C^{14}-labeled pyruvate by livers of normal and diabetic rats. *J. Biol. Chem.* **214**:525-535, 1955.
21. Foster, J. M., and Villee, C. A. Pyruvate and acetate metabolism in isolated rat diaphragm. *J. Biol. Chem.* **211**:797-814, 1954.
22. Beatty, C. H., and West, E. S. Effect of succinic and malic acids and fructose on ketosis in alloxan-diabetic rats. *J. Biol. Chem.* **215**:661-668, 1955.
23. Ungar, I., Gilbert, M., Siegel, A., Blain, J. M., and Bing, R. J. Studies on myocardial metabolism. IV. Myocardial metabolism in diabetes. *Am. J. Med.* **18**:385-396, 1955.
24. Renold, A. E., Hastings, A. B., Nesbett, F. B., and Ashmore, J. J. Studies on carbohydrate metabolism in rat liver slices. IV. Biochemical sequence of events after insulin administration. *J. Biol. Chem.* **213**:135-146, 1955.
25. Chernick, S. S., and Chaikoff, I. L. Insulin and hepatic utilization of glucose for lipogenesis. *J. Biol. Chem.* **186**:535-542, 1950.
26. Hill, R., Baker, N., and Chaikoff, I. L. Altered metabolic patterns induced in normal rat by feeding adequate diet containing fructose as sole carbohydrate. *J. Biol. Chem.* **209**:705-716, 1954.
27. Hers, H. G. Conversion of fructose-1-C^{14} and sorbitol-1-C^{14} to liver and muscle glycogen in rat. *J. Biol. Chem.* **214**:373-381, 1955.
28. Wick, A. N., Sherrill, J. W., and Drury, D. R. Metabolism of fructose by extra hepatic tissues. *Diabetes* **2**:465-468, 1954.
29. Sarett, H. P., and Snipper, L. P. Comparison of fructose and glucose in diet of alloxan-diabetic rats. *J. Nutrition* **52**:525-540, 1954.
30. Geiger, E., and Pinsky, J. J. Utilization and nitrogen-sparing effect of fructose in alloxan diabetic rats. *Metabolism* **4**:166-173, 1955.
31. Moorhouse, J. A. Correction of metabolic defects in diabetes mellitus by continuous fructose feeding. *J. Lab. & Clin. Med.* **46**:934, 1955.
32. Mendeloff, A. I., and Weichselbaum, T. E. Role of human liver in assimilation of intravenously administered fructose. *Metabolism* **2**:450-458, 1953.
33. Albanese, A. A., Higgons, R. A., Orto, L., Belmont, A., and DiLallo, R. Effect of age on utilization of various carbohydrates by man. *Metabolism* **3**:154-159, 1954.
34. Daughaday, W. H., and Larner, J. Renal excretion of inositol in normal and diabetic human beings. *J. Clin. Investigation* **33**: 326-332, 1954.
35. Gurin, S. Normal lipid metabolism. *Diabetes* **4**:182, 1955.
36. Hausberger, F. X., Milstein, S. W., and Rutman, R. J. Influence of insulin on glucose utilization in adipose and hepatic tissues in vitro. *J. Biol. Chem.* **208**:431-438, 1954.
37. Hutchens, T. T., Van Bruggen, J. T., Cockburn, R. M., and West, E. S. Effect of fasting upon tissue lipogenesis in intact rat. *J. Biol. Chem.* **208**:115-122, 1954.
38. Shaw, W., and Gurin, S. Relationship of glycolysis to lipogenesis in aqueous extracts of liver. *Arch. Biochem.* **47**:220-223, 1953.
39. Balmain, J. H., and Folley, S. J. Further observations on in vitro stimulation by insulin of fat synthesis by lactating mammary gland slices. *Biochem. J.* **49**:663-671, 1951.
40. Allen, A., Friedmann, B., and Weinhouse, S. Tissue preferences for fatty acid and glucose oxidation. *J. Biol. Chem.* **212**:921-933, 1955.
41. Hotta, S., Hill, R., and Chaikoff, I. L. Mechanism of increased hepatic cholesterogenesis in diabetes: its relation to carbohydrate utilization. *J. Biol. Chem.* **206**:835-844, 1954.
42. Van Bruggen, J. T., Yamada, P., Hutchens, T. T., and West, E. S. Lipogenesis of intact alloxan-diabetic rat. *J. Biol. Chem.* **209**:635-640, 1954.

43. Abraham, S., Chaikoff, I. L., and Hassid, W. Z. Conversion of C^{14}-palmitic acid to glucose. II. Specific glucose carbons labeled. *J. Biol. Chem.* **195**:567-581, 1952.
44. Sobel, A. E., Rosenberg, A., and Adelson, H. In vivo conversion of carotene to vitamin A in alloxan diabetes. *Arch. Biochem.* **44**:176-180, 1953.
45. Lawrence, R. T. B., Salter, J. M., and Best, C. H. Effect of insulin on nitrogen retention in hypophysectomized rat. *Brit. M. J.* **2**:437-439, 1954.
46. Sanger, R., Thompson, E. O., and Kitai, R. Amide groups of insulin. *Biochem. J.* **59**:509-518, 1955.
47. Wrinch, D. Molecules of insulin structure. *Science* **116**:562-564, 1952.
48. Elgee, N. J., and Williams, R. H. Fate of insulin in altered metabolic states. *Diabetes* **4**:8-12, 1955.
49. Haugaard, N., Vaughan, M., Haugaard, E. S., and Stadie, W. C. Studies of radioactive injected labeled insulin. *J. Biol. Chem.* **208**:549-563, 1954.
50. Elgee, N. J., Williams, R. H., and Lee, N. D. Distribution and degradation studies with insulin-I^{131}. *J. Clin. Investigation* **33**: 1252-1260, 1954.
51. Rose, S., and Nelson, J. Studies with radio-iodinated insulin. *Australian J. Exper. Biol. & Med.* **32**:429-436, 1954.
52. Lee, N. D., and Williams, R. H. Intracellular localization of labeled thyroxine and labeled insulin in mammalian liver. *Endocrinology* **54**:5-19, 1954.
53. Mirsky, I. A. Insulinase and insulinase inhibitor activity of liver. In *Ciba Foundation Colloquia of Endocrinology.* Edited by G. E. W. Wolstenholme and M. Cameron. 7 vol. Vol. 6. Boston: Little, Brown, 1953. Pp. 263-277.
54. Vaughn, M. Inactivation of insulin by enzyme from rat liver. *Biochem. et biophs. acta* **15**:432, 1954.
55. Narahara, H. T., Tomizawa, H. H., Miller, R., and Williams, R. H. Intracellular distribution of insulin-inactivating system of liver. *J. Biol. Chem.* **217**:675-684, 1955.
56. Tomizawa, H. H., and Williams, R. H. Studies on specificity of insulin-inactivating system of liver. *J. Biol. Chem.* **217**:685-694, 1955.
57. Williams, R. H. Insulin distribution and degradation. *Metabolism* **5**:128-137, 1956.
58. Elgee, N. J., and Williams, R. H. Pituitary and adrenal influences on insulin I^{131} degradation. *Am. J. Physiol.* **180**:9-12, 1955.
59. *Idem.* Effects of thyroid function on insulin-I^{131} degradation. *Am. J. Physiol.* **180**:13-15, 1955.
60. Mirsky, A., Perisutti, G., and Diengott, D. Effect of 'insulinase-inhibitor' on destruction of insulin by intact mouse. *Proc. Soc. Exper. Biol. & Med.* **88**:76-78, 1955.
61. Mirsky, I. A., Perisutti, G., and Jinks, R. Destruction of insulin by intact mice. *Endocrinology* **56**:484-488, 1955.
62. Beyer, R. W. Study of insulin metabolism in insulin tolerant strain of mice. *Acta endocrinol.* **19**:309-332, 1955.
63. Mirsky, I. A., Perisutti, G., and Diengott, D. Inhibition of insulinase by hypoglycemic sulfonamides. *Metabolism* **5**:156-161, 1956.
64. Vallance-Owen, J., and Hurlock, B. Estimation of plasma-insulin by rat diaphragm method. *Lancet* **1**:68-70, 1954.
65. Randle, P. J. Assay of plasma insulin activity by rat-diaphragm method. *Brit. M. J.* **1**:1237-1240, 1954.
66. Ottaway, J. H., and Bulbrook, R. D. Pituitary growth hormone and glucose utilization of rat diaphragm. *J. Endocrinology* **12**: 50-56, 1955.
67. Welsh, G. W., III, Henley, E. D., Williams, R. H., and Elgee, N. J. Distribution and metabolism of insulin labeled with radioactive iodine (I^{131}) in normal and diabetic subjects. *Diabetes* **5**: 15-17, 1956.
68. Cornblath, M. Reactivation of rabbit liver phosphorylase by epinephrine, glucagon and ephedrine. *Am. J. Physiol.* **183**:240-244, 1955.
69. Hubble, D. Action of glucagon on blood sugar in normal and diabetic persons. *Diabetes* **4**:197-202, 1955.
70. Haugaard, E. S., and Haugaard, N. Effect of hyperglycemic-glycogenolytic factor on fat metabolism of liver. *J. Biol. Chem.* **206**:641-645, 1954.
71. Van Italie, J. B., Morgan, M. C., and Dotti, L. B. Effect of glucagon on peripheral utilization of glucose in man. *J. Clin. Endocrinol.* **15**:28-35, 1955.
72. Elrick, H., Hlad, C. J., Jr., and Witten, T. Enhancement of peripheral glucose utilization by glucagon. *J. Clin. Investigation* **34**:1830-1838, 1955.
73. Candela, J. L. R. Inhibitory effect of pancreas extract and H-G. factor on insulin glucose uptake of isolated diaphragm. In *Ciba Foundation Colloquia of Endocrinology.* Edited by G. E. W. Wolstenholme and M. Cameron. 7 vol. Vol. 6. Boston: Little, Brown, 1953. Pp. 233-242.
74. Snedecor, J. G., DeMeio, R. H., and Pincus, I. J. Reduction by glucagon of glycogen deposition effect of insulin in rat diaphragm. *Proc. Soc. Exper. Biol. & Med.* **89**:396, 1955.
75. Pincus, I. J., Grice, M. S., Dunn, M., and Rutman, J. Z. Effect of glucagon (HGF) on deposition of muscle glycogen. *Am. J. Physiol.* **183**:413-415, 1955.
76. Young, F. G. Discussion of Candela, J. L. R.[73] Pp. 241 and 242. and 242.
77. Drury, D. R., Wick, A. N., and Sherrill, J. W. Effect of hyperglycemic factor on metabolism of glucose by extrahepatic tissues. *Diabetes* **3**:129-132, 1954.
78. Bencosme, S. A., Liepa, E., and Lazarus, S. S. Glucagon content of pancreatic tissue devoid of alpha cells. *Proc. Soc. Exper. Biol. & Med.* **90**:387-392, 1955.
79. Lazarus, S. S., Volk, B. W., and Goldner, M. G. Hyperglycemic action of pancreatic extracts from duct-ligated, alloxanized and cobalt-treated dogs. *Metabolism* **3**:449-455, 1954.
80. Volk, B. W., Goldner, M. G., and Frank-Crowley, H. Effect of prolonged growth hormone administration on pancreatic alpha cells in normal and hypophysectomized rats: use of modification of Davenport's silver impregnation method. *Metabolism* **4**:491-502, 1955.
81. Goldner, M. G., Jauregui, R. H., and Weisenfeld, S. Disappearance of HGF from insulin after liver perfusion. *Am. J. Physiol.* **179**:25-28, 1954.
82. Campbell, J., Chaikof, L., and Davidson, I. W. F. Metahypophyseal diabetes produced by growth hormone. *Endocrinology* **54**: 48-58, 1954.
83. Galansino, G., Weinstein, H. R., Magill, A. M., and Foà, P. P. Rats chronically treated with glucagon. *Am. J. Physiol.* **180**:27-30, 1955.
84. Root, M. A. Effect of chronic administration of glucagon to rats and rabbits. *Proc. Soc. Exper. Biol. & Med.* **87**:108-110, 1954.
85. Staub, A., and Behrens, O. K. Glucagon content of crystalline insulin preparations. *J. Clin. Investigation* **33**:1629-1633, 1954.
86. Lazarus, S. S., and Volk, B. W. Studies on hypoglycemia responsiveness. *Metabolism* **2**:500-509, 1953.
87. Kenny, A. J. Extractable glucagon of human pancreas. *J. Clin. Endocrinol.* **15**:1089-1105, 1955.
88. Alivisatos, J. G., and McCullagh, E. P. Studies with glucagon in patients with insulin sensitivity. *J.A.M.A.* **159**:1098-1105, 1955.
89. Volk, B. W., Lazarus, S. S., and Lew, H. Effect of various hormones on rate of decline of blood sugar in modified glucose insulin tolerance test. *Metabolism* **4**:10-18, 1955.
90. Campbell, J., Munroe, J. S., Hausler, H. R., and Davidson, I. W. F. Effects of growth hormone in diabetic dogs. *Endocrinology* **53**:549-563, 1953.
91. Bondy, P. K. Acute effects of purified crystalline pituitary growth hormone on normal human beings. *Yale J. Biol. & Med.* **26**: 263-274, 1954.
92. Shorr, E., Carter, A. C., Kennedy, B. J., and Smith, R. W., Jr. Metabolic studies on effects of crystalline growth hormone (somatropin) in man. *Diabetes* **3**:94-98, 1954.
93. Weil, R. Metabolic function of pituitary growth hormone. *Arch. Int. Med.* **95**:739-760, 1955.
94. Fasoli, A., Magid, E. B., Glassman, M. D., and Foà, P. P. Serum lipoproteins in experimental diabetes. III. Effect of anterior pituitary growth hormone. *Proc. Soc. Exper. Biol. & Med.* **87**:167-169, 1954.
95. Greenbaum, A. L., and McLean, P. Mobilization of lipid by anterior pituitary growth hormone. *Biochem. J.* **54**:407-413, 1953.
96. *Idem.* Influence of pituitary growth hormone on catabolism of fat. *Biochem. J.* **54**:413-424, 1953.
97. Abelove, W. A., and Paschkis, K. E. Comparison of diabetogenic action of cortisone and growth hormone in different species. *Endocrinology* **55**:637-654, 1954.
98. De Bodo, R. C., and Sinkoff, M. W. Growth hormone and carbohydrate metabolism. *Diabetes* **3**:87-93, 1954.
99. Boutwell, R. K., and Chiang, R. Acute effect of cortisone treatment on utilization of glucose by mouse. *Arch. Biochem.* **50**:461-472, 1954.
100. Hausberger, F. X., and Hauberger, B. C. Over-all glucose utilization in steroid diabetic guinea pigs. *Am. J. Physiol.* **183**:302-306, 1955.
101. Franckson, J. R. M., et al. Observations sur le diabète stéroide expérimental du rat. *Acta endocrinol.* **14**:153-169, 1953.
102. Burns, T. W., et al. Studies on interdependent effects of stress and adrenal cortex on carbohydrate metabolism in man. *J. Clin. Investigation* **32**:781-791, 1953.
103. Holten, C., and Lundback, K. Metabolic and renal diabetes after administration of ACTH. *Bull. Schweiz. Akad. med. Wissensch.* **8**:82-99, 1952.
104. Lazarus, S. S., and Bencosme, S. A. Alterations of pancreas during cortisone diabetes in rabbits. *Proc. Soc. Exper. Biol. & Med.* **89**:114-118, 1955.
105. Houssay, B. A., Rodriguez, R. R., and Cardeza, A. F. Prevention of experimental diabetes with adrenal steroids. *Endocrinology* **54**:550-552, 1954.
106. Ingle, D. J., Nezamis, J. E., and Humphrey, L. M. Effect of adrenal cortical extract and steroids upon glucose tolerance of eviscerated rats. *Proc. Soc. Exper. Biol. & Med.* **84**:45-47, 1953.
107. Amatuzio, D. S., Schultz, A. L., Vanderbilt, M. J., Rames, E. D., and Nesbitt, S. Effect of epinephrine, insulin, and hyperthyroidism on rapid intravenous glucose tolerance test. *J. Clin. Investigation* **33**:97-102, 1954.
108. Goddard, J. W., and Sommers, S. C. Thyroid stimulation in diabetes mellitus. *Diabetes* **3**:383-388, 1954.
109. Rodriguez, R. R. Alloxan diabetes in rat: recovery following estrogen treatment. *Endocrinology* **55**:1-9, 1954.
110. Sturtevant, F. M., Calvin, L. D., and Fuller, N. E. Relationship among glycuria, food intake and body weight in alloxan diabetes. *Metabolism* **3**:262-267, 1954.
111. Green, M. N., Beaser, S. B., and Seligman, A. M. Effect of alpha methyl stilbene on blood sugar and on insulin content of pancreas of animals. *J. Lab. & Clin. Med.* **44**:710-714, 1954.
112. Bergqvist, N. Gonadal function in male diabetics. *Acta endocrinol.* **15** (Supp. 18):1-29, 1954.
113. *Idem.* Gonadal function in female diabetics. *Acta endocrinol.* **15** (Supp. 19):1-20, 1954.
114. Steinberg, A. G. Heredity and diabetes. *Eugenics Quart.* **2**:26-30, 1955.
115. *Idem.* Inheritance and anticipation in diabetes mellitus in relation to carbohydrate metabolism during pregnancy. *Diabetes* **4**: 126-132, 1955.
116. Landau, B. R., and Renold, A. E. Distribution of alloxan in rat. *Diabetes* **3**:47-50, 1954.
117. Wrenshall, G. A., Andrus, S. B., and Mayer, J. High levels of pancreatic insulin coexistent with hyperplasia and degranulation of beta cells in mice with hereditary obese-hyperglycemic syndrome. *Endocrinology* **56**:335-340, 1955.
118. Wrenshall, G. A., and Bogoch, A. Weight and extractable insulin of pancreas in adult nondiabetic man. *J. Clin. Endocrinol.* **15**: 435-441, 1955.
119. Wrenshall, G. A., Hartroft, W. S., and Best, C. H. Insulin extractable from pancreas and islet cell histology: comparative studies in spontaneous diabetes in dogs and human subjects. *Diabetes* **3**:444-452, 1954.

120. Hartroft, W. S., and Wrenshall, G. A. Correlation of beta-cell granulation with extractable insulin of pancreas: studies in adult human diabetics and nondiabetics. *Diabetes* **4**:1-7, 1955.

121. Barrnett, R. J., Marshall, R. B., and Seligman, A. M. Histochemical demonstration of insulin in islets of Langerhans. *Endocrinology* **57**:419-438, 1955.

122. Bencosme, S. A. Cytology of islet cells in alloxan diabetic rabbits. *Am. J. Path.* **31**:1149-1163, 1955.

123. Faller, A. Die cytotoxische Wirkung von Alloxan und Dialursäure auf die Zellen der Pancreasinseln und die dadurch bedingten Regenerationserscheinungen. *Bull. Schweiz. Akad. med. Wissensch.* **10**:221-238, 1954.

124. Hartmann, A. F., Sr., Wohltmann, H. J., and Hartmann, A. F., Jr. Dietary fructose in children with diabetes mellitus. *J. Pediat.* **45**:27-50, 1954.

125. Kelly, H. G., Rao, P. T., and Jackson, R. L. Insulin requirements of children with diabetes mellitus maintained in good control. *Am. J. Dis. Child.* **89**:31-41, 1955.

MEDICAL INTELLIGENCE

RISK OF CATHETERIZATION OF THE LEFT SIDE OF THE HEART*

G. H. LAWRENCE, M.D.†

ANN ARBOR, MICHIGAN

ALTHOUGH catheterization of the left side of the heart has provided necessary and significant information concerning lesions of the aortic and mitral valves, there has been an understandable concern about its associated morbidity and mortality. One worries about the dangers of bleeding from the atrium or the nearby vascular structures, which might be inadvertently entered. Because experience in a given clinic is as yet limited it has seemed important to accumulate the combined experience of morbidity and mortality encountered by those interested in this helpful diagnostic procedure. It should be added that all observers have found the procedure useful in the preoperative evaluation of valvular disease. The technic and its interpretation have been described elsewhere.[1-6] Table 1 summarizes the 832 cases comprising this composite series.

DISCUSSION

It is of interest that the 3 fatal cases occurred early in each investigator's experience. Björk[9] states that his patient died when an associated aortic aneurysm was accidentally punctured, the cause of death being exsanguination. In Blakemore's[11] case a hemopericardium developed that he believed could have been better handled by pericardicentesis than the thoracotomy that was performed. Bailey's[12] patient apparently died of unknown causes on the day after catheterization. I vividly remember a patient who died from proved pulmonary embolus one day before a scheduled catheterization, indicating the risk inherent in the study of patients who are so severely ill.

The other 4 cases in which hemopericardium and hemothorax developed were treated successfully by needle aspiration. Minimal pneumothorax occurred in 10 cases in this combined series, but in no case was definitive therapy necessary.

CONCLUSIONS

In conclusion catheterization of the left side of the heart by the transbronchial or transthoracic route appears to be associated with a minimal and often avoidable risk, which is far outweighed by the significant data concerning valvular disease that are obtained. The procedure appears to be indicated in the evaluation of patients suspected of having equivocal mitral-valve disease until a definitely satisfactory procedure for the relief of mitral insufficiency is developed. It serves as a useful objective evaluation of patients who are doing poorly after technically difficult mitral-valve surgery if reoperation is considered. Finally, it is a direct method of selecting patients with aortic stenosis for valvotomy. Postoperatively, one may obtain an accurate estimate of the relief of this stenosis.[13]

TABLE 1. *Morbidity and Mortality of Left-Sided Cardiac Catheterization.*

SOURCE OF DATA	NO. OF CASES	METHOD	CASES WITH COMPLICATIONS	DEATHS
Morrow[7]	200	Transbronchial	—	—
Allison[8]	157	Transbronchial	—	—
Osaka[9]	100	Transthoracic	—	—
Björk[9]	150	Transthoracic	2 (hemoperi-cardium)	1
Kent[10] & Fisher[5]	100	Transthoracic	1 (hemoperi-cardium)	—
Lawrence et al.[6]	66	Transthoracic	1 (hemo-thorax)	—
Blakemore[11]	30	Transthoracic	1 (hemoperi-cardium)	1
Bailey[12]	29	Transthoracic		1
Totals	832		5	3

REFERENCES

1. Björk, V. O., Malmström, G., and Uggla, L. G. Left auricular pressure measurements in man. *Ann. Surg.* **138**:718-725, 1953.
2. Björk, V. O. Direct pressure measurement in left atrium, left ventricle and aorta. *Acta chir. Scandinav.* **107**:466-478, 1954.

*From the Department of Surgery, University of Michigan Medical School, and the Veterans Administration Hospital.

†Assistant professor of surgery, University of Michigan Medical School.

3. Björk, V. O., and Malmström, G. Left heart catheterization. *Circulation Research* **2**:424, 1954.
4. *Idem.* Diagnosis of aortic stenosis. *Am. Heart J.* **50**:303-307, 1955.
5. Fisher, D. L. Use of pressure recordings obtained at transthoracic left heart catheterization in diagnosis of valvular heart disease. *J. Thoracic Surg.* **30**:375-396, 1955.
6. Lawrence, G. H., Zimmerman, H. B., Bercu, B. A., and Bunford, T. H. Evaluation of mitral and aortic valvular disease by heart catheterization. *Surg., Gynec. & Obst.* **101**:558-562, 1955.
7. Morrow, A. C. Personal communication.
8. Allison, P. R. Personal communication.
9. Björk, V. O. Personal communication.
10. Kent, E. M. Personal communication.
11. Blakemore, W. S. Personal communication.
12. Bailey, C. P. In discussion of Fisher.[5]
13. Lawrence, G. H., and Reichert, R. E., Jr. Unpublished data.

JOHN BLACKALL'S OBSERVATIONS ON THE RELATION BETWEEN NUTRITIONAL DEPRIVATION AND "WET" BERIBERI

MAURICE B. STRAUSS, M.D.*

BOSTON

EIJKMAN is generally credited with the discovery in 1897 that the polyneuritic or "dry" form of beriberi is a disorder of defective nutrition. To be sure, he was unwilling to advance so heretical a doctrine and instead suggested that foods such as polished rice, being overrich in starch, produced a substance in the gastrointestinal tract that was poisonous to nerve cells and for which the outer layers of rice acted as an antidote.

It appears, however, that eighty-three years earlier, Dr. John Blackall,[1] "physician to the Devon and Exeter Hospital, and to the Lunatic Asylum, near Exeter," had a clear concept of the nature and treatment of dropsical or "wet" beriberi:

> My friend, Mr. Johnson, a surgeon of this city, and a practitioner of very accurate observation, informs me, that he was witness to a striking solution of the disease on board the Asia East-Indiaman, off Canton. Towards the conclusion of the voyage, the sailors had been attacked with dropsical symptoms, coming on very suddenly, and without those signs which are thought strictly to characterize scurvy, sponginess of the gums, and petechiae. This disorder was attributed, no doubt with great reason, to the use of damaged rice, upon which, circumstances not necessary to detail, had reduced them in a great measure to subsist. On their arrival in port, the principal improvement in their diet was well-fermented bread, which operated as a very active diuretic within twenty-four hours after they had begun its use; and no doubt remained in the minds of any of the sick, what it was that performed the cure. Those who preferred the native vegetable acids did not obtain the same immediate benefit. (In a collection of papers on the Diseases of Lascars in long voyages, published by Dr. Hunter, Calcutta, similar symptoms are described, certainly very nearly resembling the sea-scurvy, but marked perhaps by less of a putrid acrimony. It is, indeed, reasonable to suppose, that various depravations of food should produce disorders differing from each other in some respects, although they have a general character of resemblance. There seems in them usually a great tendency to dropsical swellings; and this consideration may serve to illustrate the nature of dropsy itself.)
>
> This is an example of a remarkable diuretic effect produced by an article of diet apparently very simple, but happily chosen. It is not, however, to the literal adoption of such a practice, but to the principle of it, that I wish to direct the attention of the reader, and to that facility of cure which results in scorbutic dropsies from an appropriate chemical corrective. How far this principle may be extended to common cases, in which there has been no extraordinary error of diet, and whether in fact there be in them any acrimony of the blood to be corrected, or altered texture to be resolved, is not very easy to determine. If the general circumstances of the distemper, have made such a state probable in the opinion of many able physicians, it is rendered more particularly so by the discovery of the coagulable nature of the urine, which would argue at least an altered texture of the lymph, and possibly some new saline matters favouring its solution. These opinions, if fully proved, would lead to a beautiful simplicity of cure; a persuasion of their possible truth may induce us to look with a favourable eye, particularly in cachectic cases, on those mild, almost dietetic remedies, which correct whilst they evacuate, or rather evacuate by correcting, and to which mineral and violent drugs have perhaps too universally succeeded.

*Professor of clinical medicine, Boston University School of Medicine; chief, Medical Service, Boston Veterans Administration Hospital.

John Blackall (1771-1860) took his M.D. degree at Oxford in 1797. Born in Exeter, he spent most of his professional career there, generally being regarded as the outstanding physician in that part of England.[2] It may be noted that he recognized the fact that dropsy is often associated with albuminuria and diseased kidneys that are incapable of producing a concentrated urine.

REFERENCES

1. Blackall, J. *Observations on the Nature and Cure of Dropsies, and Particularly on the Presence of the Coagulable Part of the Blood in Dropsical Urine: To which is added an appendix, containing several cases of angina pectoris, with dissections, etc.* First American, from the third London edition. 274 pp. Philadelphia: J. Webster, 1820. Pp. 217-219.
2. Major, R. H. *A History of Medicine.* Vol. 2. Springfield, Illinois: Thomas, 1954. Pp. 705 and 706.

BY THE LONDON POST

Problems of the Elderly — Public-Health Centenary — Crash Helmets and Motorcyclists

JOHN LISTER, M.D.

LONDON, ENGLAND

THE Minister of Health recently said that the problems of the aged should be a challenge to the public conscience. Improvements in medicine had added years to life, and he believed that the aim should now be to add life to those years.

For many elderly persons the provision of suitable living accommodation presents the major problem. The census of 1951 showed that the number living entirely alone is increasing steadily and that most of such one-person households are feminine. In 1951, 3 of every 10 spinsters and widows over the age of sixty lived alone. Many other maiden aunts and widowed grandmothers live in the homes of their

married children and are often the unwilling cause of discomfort to themselves and their kin.

Ideally, and so long as health permits, the elderly woman wants to be cheaply housed, near but not with her family. She wants to retain her independence and her own possessions and yet to be near enough to remain within the family circle, so being able both to give and to receive help during illness and other family crises.

Unfortunately, a relatively minor illness or disability of old age too often takes the elderly woman into hospital, and because of the lack of suitable accommodation for her outside, she may easily become a permanent resident in a hospital ward. Indeed, the Minister of Health believes that there are many thousands of old people in hospital wards who, if public conscience were fully aroused, could be living with their families, in old people's bungalows or in old people's hostels.

Many efforts are being made to provide suitable accommodation for such elderly women. The practice of including special bungalows or flats for the elderly in new estates is growing. In some places voluntary organizations have acquired large houses and converted them into suitable dwellings for a number of independent old people. In Liverpool the Women's Voluntary Services has co-operated with local authorities in such a project. The local authority acquires and converts each house into bed-sitting rooms equipped with modern heating appliances, the kitchens and bathrooms being shared by two or three women. Tenants furnish their own rooms, have their own door keys and live independently. The house is managed by the Women's Voluntary Services, and an elderly woman installed as warden gives her services in lieu of rent.

As far as elderly men are concerned, the problem is often to keep them in healthy and happy employment. This subject was recently discussed at the annual conference of the local advisory councils on occupational health, which stressed the fact that the majority of men would like to work until the late sixties if suitable work could be found. Unfortunately, this is not always possible. Le Gros Clark reported that not more than 15 per cent of men over sixty-five years of age can hope to remain gainfully employed in heavy industry although a larger proportion can carry out lighter duties where pace need not be a primary consideration. In many of the professions it has become customary to retire at sixty-five. In the medical profession this retiring age has been fixed for hospital medical staff, although there is no retiring age for general practitioners, and many consultants remain in practice until an advanced age. In this respect Dr. Philip Ellman, in an interesting letter to the *British Medical Journal,* recalled that Lord Dawson, Lord Horder, Sir Humphrey Rolleston and Sir Almroth Wright were all octogenarians and active in medical practice until their deaths, and that octogenarians who are living today and who retain an active interest include Sir Henry Dale and Sir Robert Hutchison. Dr. Ellman was able to name several well known members of the profession who became nonagenarians and yet retained their interest until the end. This group included Sir Charles Sherrington, Dr. Graham Steel and Sir Thomas Barlow; Dr. Frederick Parkes Weber, whose father reached the age of ninety-five, is still keenly interested in medicine at the age of ninety-three. Until he was nearly ninety he was a constant figure at the meetings of the Royal Society of Medicine, and although he is no longer able to attend, his mind remains alert and his contributions to the literature continue.

It is clear that these octogenarians and nonagenarians have only been slightly troubled by the problems of old age, and all seem to have overcome these problems by the fact that they have retained an active interest in life.

* * *

The Society of Medical Officers of Health recently held its centenary celebrations. It was in 1855 that the appointment of medical officers of health was made compulsory in the various districts of London, and in the following year the Metropolitan Association of Medical Officers of Health was formed.

At that time there were few medical officers of health outside London, but as their numbers increased, several provincial associations were formed; in 1873 they all amalgamated under the name by which the Society is now known. The purpose of the association is: "to promote the advancement of public health in every branch."

The centenary celebrations included an oration by Lord Adrian, O.M., a historical exhibition and a series of panel discussions. Lord Adrian pointed out that the concept of public health has not only prolonged lives but also transformed them. Looking to the future, he suggested fields for new effort. In particular he spoke of the need for research in the field of mental welfare. He said that contemporary society can afford to be more sympathetic to mental inadequacy than was possible in the past. Speaking of crime and delinquency, he observed that men have come to doubt the efficacy of punishment in this world or of the threat of it in the next as a deterrent to faulty behavior. The psychoanalysts have convinced everyone that the early experience of the infant is the most important controllable factor in determining its future chances of happiness but have not outlined the practical measures required. Thus, it is still difficult to decide how long a baby should be left to cry and how often it should be fed to ensure its future mental welfare. Lord Adrian said there was still a need for the expansion of the mental-health services and for continued review of the methods of research in this field.

The panel discussions covered such topical subjects

as smoke abatement, poliomyelitis and the importance of increasing the co-operation between general practitioners and the medical officers of health. The historical exhibition arranged by Dr. Ashworth Underwood at the Wellcome Building reviewed the history of preventive medicine from earliest times. The many excellent demonstrations provided not only an illustration of the amazing advances of the last century but also a stimulus for future efforts in the public-health field.

* * *

The motorcyclist continues to share in the rising toll of the road. In 1954 there were more than 1,000,000 motorcycles on the roads of Great Britain, and in that year there were 4447 deaths from road accidents, a quarter of which involved motorcyclists or their passengers.

A recent report from the Accident Service of the Radcliffe Infirmary, Oxford, and the Military Hospital for Head Injuries, Wheatley, reviewed the problem of head injuries in motorcyclists and discussed the value of crash helmets in minimizing their effects.

In 1941 the wearing of crash helmets was made compulsory for all Army motorcyclists on the advice of the late Sir Hugh Cairns, and this measure was certainly one of the major factors in the fall in fatal motorcycle accidents over the next five years. Such accidents, however, still account for a third of all deaths from head injuries, and the authors of the present review believe that this figure could be much reduced if a higher proportion of civilian motorcyclists wore crash helmets. At present, not more than 30 per cent do so. It has been clearly shown that efficient crash helmets will prevent minor concussion and lessen the effects of more severe injuries.

The most satisfactory design of crash helmet is being investigated by the Road Research Laboratory, and the British Medical Association is carrying out tests on the types at present available. The Oxford workers believe that the outer shell should be tough and not brittle, and impregnated wood pulp is the most useful material at present available. The internal padding is highly important — it should absorb the maximum energy and reduce the maximum force to the head. To ensure this, good-quality Sorbo rubber should be incorporated all around the interior of the helmet.

Crash helmets, of course, will not prevent accidents, and head injury is by no means the only hazard run by the motorcyclist. On the other hand they do make motorcycling safer, and their use should be encouraged by parents, employers and motorcycle clubs. In addition improved training schemes for motorcyclists are required, and the provision of efficient accident services in hospitals is essential.

CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 42301

PRESENTATION OF CASE

First admission. A forty-three-year-old executive entered the hospital because of fatigue.

Two years previously there was an episode of intense jaundice that was associated with pruritus, slight nausea, abdominal tenderness in the right upper quadrant, dark urine, clay-colored stools and a loss in weight of 8 to 10 pounds. He was bed ridden for ten weeks and "run down" for the subsequent six to eight months. One year later there was a recurrent similar episode of jaundice that lasted for six weeks. The pruritus persisted. Subsequently, he felt "exhausted" most of the time.

During the eight years before admission he had numerous furuncles, for which he received injections of autogenous and commercial staphylococcus toxoid as well as some medicine that contained tin. During the seven years before entry there were occasional episodes of pain in the left arm that were precipitated by overactivity, cold or flatulence and relieved by nitroglycerin. After the first episode of jaundice the pain worsened and at times also occurred substernally. Flatulence was caused by overindulgence in fatty foods. During the four months before admission there was increased urinary frequency with urgency and burning on urination.

Physical examination showed a well nourished man with numerous scars of healed furuncles over the entire body. There was no lymphadenopathy. Examination of the heart revealed a Grade 1 apical systolic murmur. The liver, which was palpable 3 cm. below the right costal margin, was tender after exercise. The upper border of liver dullness was at

the fifth intercostal space. The spleen was not felt. Moderate tenderness was noted in the left costovertebral angle. Rectal examination was negative.

The temperature was 98°F., the pulse 80, and the respirations 20. The blood pressure was 130 systolic, 80 diastolic.

The urinary sediment contained many bacteria per high-power field. Examination of the blood revealed a hemoglobin of 15.5 gm. per 100 ml. and a white-cell count of 9400. The sedimentation rate was 32 mm. per hour. The nonprotein nitrogen, the total protein, the albumin, the globulin, the bilirubin and the fasting blood sugar were normal. The prothrombin content was 100 per cent. The bromsulfalein retention was 20 per cent after thirty-five minutes. X-ray films of the chest, a Graham test and an upper gastrointestinal series were normal. An electrocardiogram showed a normal sinus rhythm at a rate of 75; the PR interval was 0.13 second; the axis was normal; the T waves were upright in Leads 1 and 2, flat in Lead 3, upright in Leads CF_2 and CF_4 and low upright in Lead CF_5.

The patient was discharged on the seventh hospital day on a high protein and carbohydrate diet with vitamins.

Second admission (ten weeks later). In the interval he continued to feel fatigued until four weeks before entry, when the intake of vitamins was increased and he took liver extract orally. Subsequently, there was less fatigue; the appetite improved; the itching was not as severe, and the episodes of pain in the arm were not as frequent. There was still urinary frequency.

Physical examination showed no change.

The urine was normal. Examination of the blood revealed a hemoglobin of 15 gm. per 100 ml. and a white-cell count of 18,800, with 76 per cent neutrophils. A subsequent white-cell count was 8100. The sedimentation rate was 22. The nonprotein nitrogen was 30 mg., the total protein 8.22 gm., the albumin 4.87 gm., the globulin 3.35 gm., the bilirubin 1.7 mg., the cholesterol 312 mg., and the phosphorus 2.9 mg. per 100 ml. The alkaline phosphatase was 13.7 units. The prothrombin content was 100 per cent. Cephalin flocculation was + in 48 hours. The thymol turbidity was 8.2 units, and the flocculation ++++. The bromsulfalein retention was 15 per cent. An electrocardiogram showed no significant change.

An operation was performed on the third hospital day.

Differential Diagnosis

Dr. Myles P. Baker*: At the time of the first admission this forty-three-year-old man had a two-year story of fatigability dating from a protracted illness characterized by jaundice and pruritus. The only important positive finding on physical examination was a definitely enlarged liver, which was tender after exercise. He was not jaundiced. The only abnormal laboratory finding was the bromsulfalein retention of 20 per cent on a thirty-five-minute test. He presented the picture of an unhealed and therefore probably progressive infectious hepatitis of viral origin, which certainly was one possibility for diagnosis and was the one with which he was sent off on supportive therapy. It is important that this man without clinical jaundice had been itching without any palpable skin lumps — a symptom that to me certainly suggests intrahepatic disease.

When he returned to the hospital ten weeks after discharge, the same physical findings and a few new abnormal laboratory findings were noted as follows: an increase in the serum globulin level, the finding of pronouncedly positive thymol flocculation and increased thymol turbidity (the last tests had not been done on the first admission), a definite elevation of the alkaline phosphatase, which was not recorded on the first admission, the appearance of a mild degree of bilirubinemia, slight elevation in the serum cholesterol level and continued bromsulfalein retention. The globulin was raised; increases of abnormal serum globulins make for a positive thymol turbidity and flocculation. The elevation of the serum alkaline phosphatase is in some mysterious way from the point of view of function related to intrahepatic obstruction below, sometimes just below, the terminal biliary tracts. This, of course, is well known to be an elevation that occurs in lower common-bile-duct obstruction and appears earlier than the hyperbilirubinemia. The really negative cephalin flocculation test to go with the positive thymol flocculation test is not surprising, because the patient may well have had an intrahepatic disease that was not associated with active necrosis of the liver parenchyma, a process that in some way interfered with the development of the protective substance that makes the cephalin flocculation negative. I can assume, therefore, that I am not dealing with acute hepatitis in the sense of parenchymal damage at the second admission.

To go back to the clinical history, this man in the first illness was sick much longer than most patients with viral hepatitis are. Neefe,[1] whose experience with infectious hepatitis is one of the large ones on record, says that most of the unfortunate persons whose livers have trouble in healing after infectious hepatitis have relapses within six months. Perhaps he is speaking of those who sustained less of a blow in the initial illness than this patient did. He makes the point that when a patient who has had infectious viral hepatitis has a recurrence of jaundice and all that goes with it at the end of about a year's time, one should be suspicious of the initial diagnosis of hepatitis. I should, therefore, consider something other than infectious hepatitis as the original condition in a patient having as late a recurrence of jaundice as this man had — despite my belief that he

*Physician, Massachusetts General Hospital.

had had nonhealing, progressive, chronic, originally viral hepatitis.

The possibility of extrahepatic common-bile-duct obstruction, by granulomas or lymphoma, should be considered. I think most of the causes of obstruction could give this picture, but I shall have to dismiss them for lack of evidence. Sarcoidosis of the liver rarely causes jaundice. Such cases of extrahepatic and intrahepatic lymphoma give the same sort of liver-function tests that this man had on the second admission — namely, an increase in serum globulin and a positive thymol flocculation.

The question is what one would do first with this tired, icteric person with changing (for the worse) liver-function tests and fatigability. Can extrahepatic biliary obstruction be ruled out? Were calculi in the common duct missed? It seems unlikely that he had gallstones because the Graham test on the first admission was negative. Can exploration be avoided? It is interesting in reading over the early reported cases of so-called cholangiolitic hepatitis to note how many of them were explored. Liver biopsy may help one be sure that there is no hepatitis. Will a liver biopsy tell the story? I am not sure that it always will. The picture obtained at liver biopsy that is said to be characteristic of cholangiolitic hepatitis must look a good deal like that above an extrahepatic obstruction. I think that if I were responsible for the patient I should ask for a biopsy of the liver. Such a procedure seems to me reasonable; I think that was the operation that was done. My belief is that the patient had a chronic hepatitis of viral origin that progressed to present the picture of perilobular fibrosis, an early postnecrotic cirrhosis. It probably was not cholangiolitic hepatitis and cirrhosis, because he had not had the amount of persistent jaundice that such patients have, but it may well have been a first cousin to that.

The other possibility is that he had been harboring a lymphoma for a number of years. I doubt very much if he was explored. If he was, I do not believe that the surgeons found benign obstruction of the common bile duct and think that the diagnosis was possibly made by liver biopsy at operation.

Clinical Diagnoses

Postnecrotic cirrhosis with esophageal varices.
Infectious hepatitis.
Coronary occlusion, old.

Dr. Myles P. Baker's Diagnoses

Chronic viral hepatitis.
Early postnecrotic cirrhosis.

Anatomical Diagnoses

Chronic viral hepatitis.
Postnecrotic cirrhosis.
Esophageal varices.
Fibrocongestive splenomegaly.
Ascites.
Coronary occlusion, left circumflex, old.

Pathological Discussion

Dr. Austin L. Vickery: This is an unusual case from several standpoints, not the least of which is the fact that the pathologists have willfully withheld not a mere fragment of information but a mass of data gained over a period of ten years during seventeen subsequent admissions of this patient. For the sake of brevity and expediting further discussion of this interesting case and also to give Dr. Baker opportunity for a revision of his diagnosis, I shall give a résumé of what happened from 1946, when the first liver biopsy was done, to the time this man died in 1956. During this entire period he was under the close scrutiny of Dr. Chester M. Jones and also Dr. Edward F. Bland; consequently, it is a well documented case of whatever it is. In addition, we are fortunate to have a series of liver biopsies for review and comparison. The first biopsy, obtained in 1946, was the operation during the second admission, as Dr. Baker predicted, and was interpreted as showing a typical picture of chronic persistent epidemic hepatitis by Dr. Tracy B. Mallory. The portal areas were conspicuous and infiltrated with chronic inflammatory cells, and there were focal zones of liver-cell degeneration.

During the following ten years, this patient had 17 more admissions to the hospital, all of which were related to such chronic symptoms as easy fatigability, vague abdominal and epigastric distress, malaise and angina pectoris. Two years after the first liver biopsy (and four years after the original episode of jaundice) the patient returned for a periodic hospital re-evaluation of the liver status, and during this admission a second liver biopsy was obtained. Although not definitely ill, he was not well and had been working only part time. The liver-function indexes at this time (1948) were as follows: bromsulfalein retention, 45 per cent; alkaline phosphatase, 13.1 units; cephalin flocculation, + + + and + + + + at twenty-four and forty-eight hours; and albumin-globulin ratio, 1.3 (Table 1). The liver was still tender and now enlarged 5 cm. below the costal margin. Dr. Jones commented at this time that, although there was no evidence yet of portal hypertension, the liver lesion appeared to be a "slowly progressive process."

The liver biopsy again showed the portal zones heavily infiltrated with lymphocytes, mononuclear cells and some eosinophilic leukocytes. There was also a vague suggestion of accentuated lobularity, with some increase in connective tissue. The diagnosis again was persistent chronic epidemic hepatitis with the observation that "the picture has not changed significantly since the previous biopsy" of two years before.

A PHYSICIAN: Did alcohol play a part in the picture?

DR. VICKERY: Apparently, there was never any question about that. On the advice of Dr. Jones the patient stopped a moderate alcohol intake after the initial admission.

In 1950 (two years after the second biopsy, four years after the first and six years after the initial illness with jaundice) the patient was admitted to the hospital because of fatigue and abdominal cramps. A third biopsy was obtained of the liver, which showed essentially the same features as the previous biopsies (Fig. 1). The liver was definitely larger, extending almost to the umbilicus. The liver-function tests still showed an abnormal pattern (see Table 1). There were still no signs of portal hypertension, including fluoroscopic evidence of esophageal varices.

Over the next three years, from 1950 to 1953, there were 4 more hospital admissions, principally referable to the patient's chronic invalidism and symptoms such as intermittent bouts of chronic fever, epigastric distress and general debility. He was able to work three or four hours a day, however, at his office when he was relatively symptom free; at the same time there was a slow, relentless progression of the illness, as indicated by the liver-function tests (Table 1); these studies continued to reflect a chronic smoldering hepatitis. Various clinical manifestations of hepatic cirrhosis appeared during this interval — namely, numerous spider angiomas over the trunk, liver palms and facial telangectases. However, there was still no evidence of ascites. Esophageal varices were searched for during all these admissions by fluoroscopy, but were not observed, nor had there been gastrointestinal bleeding up to this time.

In 1954 there was a definite change in the clinical course: he began to be persistently jaundiced and was never free of icterus thereafter. Esophageal varices, tarry stools and ascites all appeared in 1954; the liver-function tests were still far out of line. It is also interesting that Dr. Jones thought that the liver was slightly smaller than it had been two years previously, indicating perhaps that shrinkage due to fibrosis had begun.

Over the next two-year period, the patient gradually deteriorated, with signs of persistent liver disease and portal hypertension with ascites and bouts of melena. In January, 1956, the radiologist commented on a marked increase in the size of the esophageal varices.

The nineteenth and last admission was featured by recurrent melena and finally signs of cholemia, which was the first evidence of this that he had manifested through the entire course. He died twelve years after the initial bout of jaundice and ten years after the first admission to the hospital.

TABLE 1.

YEAR	BILIRUBIN	SERUM ALBUMIN	SERUM GLOBULIN	BROMSULFALEIN RETENTION	ALKALINE PHOSPHATASE	SERUM CHOLESTEROL	PROTHROMBIN TIME	LIVER ENLARGEMENT	SPLEEN ENLARGEMENT	ESOPHAGEAL VARICES	ASCITES	MELENA	LIVER BIOPSY
	mg./100 ml.	*gm./100 ml.*	*gm./100 ml.*	*% in 35 min.*	*units*	*mg./100 ml.*	*% normal*						
1946	1.7	4.9	3.3	15	13.7	312	100	+	0	0	0	0	+
1948	1.0	4.1	3.1	45	13.1	312	100	+	±	0	0	0	+
1950	1.4	3.9	4.1	28	31.8	—	100	+++	+	0	0	0	+
1952	1.1	4.6	3.8	24	14.7	294	—	++++	+	0	0	0	0
1954	7.8	3.3	3.8	—	19.6	—	60	+++	++	+	+	+	0
1956	19.0	2.9	3.5	—	23.4	—	55	++	++	+	+	+	+*

*Autopsy.

Before I discuss the autopsy findings, I wonder if Dr. Baker has a different idea about the diagnosis. Do you think that this would fit into your concept of a chronic hepatitis smoldering along this long?

DR. BAKER: Yes; I do.

DR. CHESTER M. JONES: I cannot add much to the story that Dr. Vickery has outlined so clearly. There was a progressive, relentless course, which was punctuated in the later years by recurrent bouts of fever. The patient was very ill in 1954, with a moderately high fever and a very tender liver. Previously, he had had bouts of fever, with tenderness of the liver, but had not had ascites that we could demonstrate. This course had all the appearance of reactivation of the process from time to time as if a smoldering fire caught the breeze and flared up. My opinion was the same as Dr. Baker's: that this was almost certainly a progressive sequence of events that followed an initial viral hepatitis. Whether or not viral activity continues in this sort of ailment is something that nobody knows. All one can do is to speculate about it. It is also possible that in this degree of liver damage the ordinary enteric bacteria, some of which undoubtedly enter the hepatic circulation by the portal system or the lymphatics, caused a secondary insult to the liver. It is interesting that the patient was ill so long before we could demonstrate varicosities. Even after they were visible he had no major hemorrhage until the day he died. He had moderate bleeding in the last months.

In the summer of 1954 he was very feeble, ran a constant temperature, had no appetite and had as-

cites. Everything else apparently had been tried so I decided to put him on corticosteroids and antibiotics. On that therapy, with a restriction of sodium, he was fairly well; the ascites disappeared, his appetite improved, and he was discharged "on his feet" and stayed "on his feet" for the next year on a small maintenance dose of corticosteroid therapy. I believe that this therapy was of some value in improving his appetite, stopping the itching and, possibly, cutting down the inflammatory process in the liver to permit more normal function.

He did have a myocardial infarction before the first admission, but he had practically no symptoms in recent years except toward the end of the course, at which time he had substernal distress when he became excited.

FIGURE 1. *Photomicrograph of the Liver Biopsy.*

DR. EDWARD F. BLAND: He was anemic at the time; that may have aggravated the heart condition.

DR. JONES: In the late months he was anemic from constant oozing of blood. Other than that the hemoglobin was at a level of 12 to 12.5 gm. per 100 ml.

DR. BLAND: He was relatively inactive.

DR. JONES: That is the other factor, of course, which permitted a reasonable degree of compensation of the cirrhosis.

DR. VICKERY: At autopsy 2700 ml. of jaundiced, clear fluid was found in the abdomen. The liver presented a striking appearance; it weighed 1950 gm., was grossly and irregularly nodular, the nodules measuring from 0.3 to 2 cm. in diameter and varying in color from yellow, to green and brown (Fig. 2). The left lobe was more fibrotic and shrunken than the majority of the right lobe. The low-power photomicrograph gives you some idea of the distribution of the hepatic fibrosis (Fig. 3). Histologically, this was considered to represent a typical example of postnecrotic cirrhosis, with the fibrotic bands encompassing nodules of varying size and with preservation

FIGURE 2. *Gross Photograph of the Liver.*

of centrolobular veins. In addition, there was bile stasis throughout the liver and focal inflammatory infiltration. Esophageal varices were demonstrated, and the small bowel contained a large amount of fresh liquid and clotted blood. The spleen was considerably enlarged, weighing 870 gm., and exhibited the usual fibrocongestive histologic picture. There was also severe coronary-artery disease, with an old occlusion of the left circumflex coronary artery.

If the findings in the liver at autopsy were the only data that we had on this case, without the good history and the previous biopsies, we should probably be content to call it ordinary postnecrotic cirrhosis and the end result of an original attack of jaundice or hepatitis of a fulminant nature ten or twelve years previously. The needle biopsies and clinical course, however, were not entirely consistent with this hypothesis because they indicated the changes of the chronically active form of hepatitis extending over a period of at least ten years. This is contrary to the usual concept of the histogenesis of postnecrotic cirrhosis.

In a recent review of liver biopsies from the large experience of the Armed Forces Institute of Pathology Smetana[2] remarked that nodular cirrhosis is an occasional consequence of viral acute hepatitis, but it is usually not considered to be the result of chronic hepatitis, although it occasionally is. The basic pathological changes as seen on serial biopsy in such cases are similar to those that follow acute nonfatal hepatitis, but with a tendency to be more focal and

less extensive. The condition, according to Smetana, is probably traceable to persistent activity of the virus of hepatitis within a relatively resistant tissue with periods of exacerbation and remission. This hypothesis would certainly be in keeping with the clinical course of the case under discussion — namely, one of initial viral hepatitis, with persistent smoldering in-

FIGURE 3. *Photomicrograph of the Liver at Autopsy.*

fection over a prolonged period and eventual scarring and regeneration of the liver. The difficult thing to reconcile with this concept is our usual explanation of the pathogenesis of postnecrotic cirrhosis. This lesion is postulated on the premise of acute extensive liver necrosis at one insult of hepatitis followed by, more or less, simultaneous regeneration in the existent framework of the necrotic liver cords. This nicely accounts for the reasonable preservation of normal liver-lobule architecture oriented about efferent veins seen in postnecrotic cirrhosis. Just how chronic hepatitis with focal necrosis and regeneration over a period of years could produce this similar end picture is open to debate. In any event, something like that seems to have occurred in this case, or perhaps we must revise our theories on the histogenesis of postnecrotic cirrhosis.

It is also of interest that in the files of the Armed Forces Institute of Pathology there is no recognized case of recurrent viral hepatitis after the completion of nodule formation. This suggests immunity to the virus at this stage.[2]

Dr. Jones, have you any other comments? I was interested in your remark that you thought that this course was consistent with postnecrotic cirrhosis.

DR. JONES: I think that it is, and I think that until one can identify and actually grow the virus, one must admit at least the possibility of continued relapsing infection. No one knows how long the virus lasts or whether it is active. I do not think that anybody can make dogmatic statements about it until the virus has been identified at different times during the illness.

REFERENCES

1. Neefe, J. R. Viral hepatitis: problems and progress to 1954. *Am. J. Med.* **16**:710-728, 1954.
2. Smetana, H. F. Histogenesis of coarse nodular cirrhosis. *Lab. Invest.* **5**:175-193, 1956.

CASE 42302

PRESENTATION OF CASE

A fifty-two-year-old woman entered the hospital because of a painful hip.

Five weeks previously she noted pain in the lower abdomen associated with constipation and followed by "grippe" with fever and malaise for several days. She felt better until one week later, when there was another episode of "grippe" with fever. Thereafter crampy, intermittent pain in the lower abdomen recurred at intervals of two to three days. During the three weeks before admission there was severe pain over the anterior aspect of the right hip, with radiation down the thigh and around the knee anteriorly. The pain prevented full extension of the knee and hip. There was also anorexia and constipation during this time, as well as a fall in weight from the usual 68 pounds to 60 pounds. Swelling of the ankles was noted three days before entry.

Physical examination revealed a tiny, emaciated woman who appeared alert and co-operative. There was no lymphadenopathy. Examination of the chest was negative. A fixed, tender abdominal mass measuring several centimeters in diameter was felt in the right lower quadrant. One observer also noted a tender, movable mass in the right flank that did not descend with respiration. Tenderness over the right hip and thigh was present. The right hip could not be extended beyond 60°, and the knee could not be extended beyond 90° because of pain. Rotation of the hip was normal. There was + + + pitting edema of the right foot. Rectal examination showed tenderness in the right vault.

The temperature was 98.2°F., the pulse 88, and the respirations 20. The blood pressure was 95 systolic, 65 diastolic.

The urine was normal. Examination of the blood revealed a hemoglobin of 9.8 gm. per 100 ml. and a white-cell count of 21,400, with 82 per cent neutrophils. The total serum protein was 5.1 gm., the albumin 3 gm., the globulin 2.1 gm., the calcium 8.6

mg. and the phosphorus 2.2 mg. per 100 ml. The alkaline phosphatase was 7.4 units. Two stool specimens gave + + + guaiac tests. X-ray films of the abdomen, lumbar spine, pelvis and hips showed no abnormalities in the bones; almost complete obliteration of all soft-tissue shadows in the pelvis and abdomen was noted. A barium-enema examination was negative. X-ray films of the chest demonstrated subapical scars bilaterally, as well as a mild increase in fibrous tissue in the lungs.

An operation was performed on the seventh hospital day.

Differential Diagnosis

Dr. Glenn E. Behringer*: The first fact that caught my attention when I read the protocol was the casual way in which it was reported that the patient lost weight from the usual 68 to 60 pounds. Was she a small person who never did weigh much?

Dr. Richard B. Cohen: She was small and never weighed more than 70 pounds.

Dr. Behringer: Was she working and active before the onset of the illness?

Dr. Cohen: Yes; she was a schoolteacher.

Dr. Behringer: The protocol also stated that there was a fixed, tender abdominal mass measuring several centimeters in diameter in the right lower quadrant. I wonder if there is any information about the exact size of the mass. Exactly where was it located? Was it fixed to the abdominal wall or to the posterior parietes?

Dr. Judson Randolph: The mass was approximately 4 by 5 cm. and seemed to be fixed to the inner pelvis rather than to the abdominal wall.

Dr. Behringer: During the illness in which she was confined to her home for five weeks did she receive any antibiotics?

Dr. Randolph: No.

Dr. Behringer: The first thing that comes to mind in a patient with abdominal symptoms, a history of constipation associated with fever and, later, pain in the pelvis with radiation to hip and leg is carcinoma of the bowel, with bony metastases. Apparently that possibility occurred to the surgeon who was following her, for x-ray films of the spine, pelvis and hips were taken and calcium, phosphorus and phosphatase determinations were obtained. Dr. Wang, may we see the films?

Dr. C. C. Wang: The films of the chest show some pulmonary emphysema and apical scarring bilaterally. Films of the abdomen show diffuse haziness of the abdomen; the visceral outlines are poorly seen, but there is no evidence of soft-tissue masses.

Dr. Behringer: Is it not usual in an extremely thin person to see obliteration of the soft-tissue outlines because of lack of intra-abdominal fat?

*Assistant in surgery, Massachusetts General Hospital.

Dr. Wang: That is a possibility, but it may also represent some degree of ascites or neoplastic tissue or inflammatory reaction in the retroperitoneal region. The barium-enema examination demonstrates no intrinsic disease in the colon. The position of the ascending colon is somewhat unusual since it is displaced somewhat medially. There is no abnormal calcification in the right iliac fossa.

Dr. Behringer: Do you see the appendix?

Dr. Wang: No; the appendix is not visible. The films of the lumbar spine, pelvis and both hips give no evidence of bone destruction. The sacroiliac joints appear normal.

Dr. Behringer: The small bowel is not filled, is it?

Dr. Wang: No; it is not.

Dr. Behringer: We do gain from Dr. Wang the opinion that the ascending colon is displaced slightly medially. There was no evidence of disease in the bones, and the lungs were apparently normal so that I think I can rule out carcinoma of the large bowel with bony metastases. The abnormalities of the calcium, phosphorus and phosphatase may have been nutritional in origin since the patient certainly was not a hearty eater.

This previously healthy woman began to suffer from abdominal symptoms associated with cramps, fever and malaise and, two weeks after the onset of the symptoms, began to have pain in the hip radiating down the anterior surface of the thigh to the knee. This type of pain is seen in hip disease with pain referred along the obturator-nerve distribution. It is also seen in pelvic inflammatory disease associated with inflammation of the psoas muscle or fascia overlying the sheath of the obturator nerve. The presence of a palpable mass in the right lower quadrant that was tender (another observer felt a palpable mass in the right flank) and the evidence in the x-ray films of medial displacement of the ascending colon suggest that the basis of trouble was an abscess in the right iliac fossa.

A tuberculous psoas abscess is a possibility, but there was no evidence of active tuberculosis elsewhere and no evidence of disease in the spine; moreover, the patient was fifty-two years of age — a little old for this disease.

Could an abscess have arisen in the pelvic organs? There was no history of any dysfunction of the genital tract. The rectal examination revealed tenderness but no masses or other abnormality of the uterus or adnexa. A twisted ovarian cyst sometimes causes abdominal pain with radiation similar to what was described in the patient under discussion. However, the course of the illness over five weeks was not consistent with that diagnosis, and a twisted ovarian cyst certainly should have been palpated on pelvic or rectal examination in a person as thin as she was.

This leaves the gastrointestinal tract. I have speculated about the possibility of carcinoma of the colon

and discarded that. Diverticulitis with abscess is a possibility, but there were no other diverticula in the colon. A single diverticulum in the cecum is unusual. The small bowel may have been the source of such a mass. A Meckel diverticulum may have become inflamed and perforated. However, this would produce a mass further medially; moreover, the course of the illness was not typical of inflammation of a Meckel diverticulum, and the pain was not the characteristic periumbilical pain of a Meckel diverticulitis. I shall eliminate perforation of an inflamed Meckel diverticulum.

A perforation of the ileum by a foreign body might simulate this situation. Fish bones, chicken bones and toothpicks are known to perforate the small bowel in the terminal few centimeters and sometimes may cause symptoms first as a result of the inflammation accompanying the perforation and later as a result of the abscess around the perforation. This would account for the blood in the stools and the recurrent nature of the discomfort.

I inquired about treatment with antibiotics because during the past several years we have seen 2 cases in which a disease thought to be viral enteritis or "grippe" was treated at home with antibiotics and the patient later entered the hospital with a pelvic abscess in 1 case and with obstruction of the small bowel caused by inflammatory adhesions about the appendix in the other. Since this patient received no antibiotics that can be discarded. Appendicitis with abscess formation is another possibility. A retrocecal appendix, with inflammation, perforation and localized abscess formation, could account for the symptoms and signs.

The decision between abscess from perforation of the bowel by a foreign body and abscess from perforation of an inflamed appendix is difficult to make. I leaned toward perforation of the ileum by a foreign body until I saw the x-ray films. The presence of the medially displaced ascending colon makes me believe that an abscess in the right iliac fossa that was extending up the right-gutter area, perhaps retroperitoneally as a result of a perforated appendix, was at the base of the trouble.

DR. COHEN: Dr. Ropes, have you an opinion?

DR. MARIAN W. ROPES: I should agree with that diagnosis. At first I thought that the elevated alkaline phosphatase was suggestive of bone involvement, but there was no other evidence of it. I cannot explain the elevated alkaline phosphatase unless there was secondary involvement of the liver. I doubt if either infectious or cancerous involvement of the bone was present.

DR. JACOB LERMAN: Would you consider a small-bowel or appendiceal tumor such as a carcinoid that had ruptured?

DR. BEHRINGER: It crossed my mind. Carcinoid of the appendix certainly cannot be ruled out conclusively. I have ruled out disease of the small bowel because of the position of the abscess.

DR. RANDOLPH: Dr. Behringer has certainly put the facts together well. I should like to indicate what we were faced with when the patient was admitted. She was admitted on the Orthopedic Service on a very busy day with a painful hip. In giving the history she minimized the "grippe" that she had had about six weeks before admission. The intermittent abdominal pain was of such a low grade of intensity that one could easily associate it with constipation. The most important factor in the physical findings was the extremely tender hip. She had extreme discomfort in the knee even though she was not moving the hip. It became apparent that she had a mass in the right lower quadrant and involvement of the lateral femoral cutaneous nerve as indicated by decreased sensation on the lateral portion of the thigh. In addition she had unilateral pedal edema, with + + + pitting around the right ankle. The rectal examination was not revealing, but the glove specimen of stool gave a + + + guaiac test. A most striking thing about the patient was the degree of emaciation. Although she was under 5 feet and small boned, the usual weight of 68 to 70 pounds had been depleted by some 10 pounds and she exhibited a picture suggestive of pituitary cachexia or the type of emaciation one would expect in advanced carcinoma.

DR. LLOYD H. SMITH, JR.: The chemical levels are those of osteomalacia: the low phosphorus, the high alkaline phosphatase and the normal calcium for the level of the protein. These findings, with the considerable weight loss, make one wonder whether the patient had a malabsorption syndrome.

CLINICAL DIAGNOSIS

Appendiceal abscess.

DR. GLENN E. BEHRINGER'S DIAGNOSIS

Inflammation of retrocecal appendix, with perforation and abscess formation.

ANATOMICAL DIAGNOSIS

Acute and chronic inflammation of retrocecal appendix, with perforation and abscess formation.

PATHOLOGICAL DISCUSSION

DR. COHEN: Dr. Behringer was correct in his diagnosis. At operation the surgeon found a large retrocecal abscess in the center of which was a necrotic, perforated appendix. The prime symptom was undoubtedly a strongly positive psoas sign that at first oriented the clinician to the hip and lower extremity rather than to the proper site of the disease.

The New England Journal of Medicine

Official Organ of
THE MASSACHUSETTS MEDICAL SOCIETY

OWNED BY THE SOCIETY AND
PUBLISHED WEEKLY UNDER THE JURISDICTION OF THE
COMMITTEE ON PUBLICATIONS

Richard M. Smith, M.D., *Chairman*
Oliver Cope, M.D. James M. Faulkner, M.D.
Richard E. Alt, M.D. Conrad Wesselhoeft, M.D.

Joseph Garland, M.D., EDITOR

ASSOCIATE EDITORS
Thomas H. Lanman, M.D. Donald Munro, M.D.
Theodore H. Ingalls, M.D.

Robert O'Leary, ASSISTANT EDITOR
Milton C. Paige, Jr., BUSINESS MANAGER

EDITORIAL BOARD
Henry R. Viets, M.D. J. Englebert Dunphy, M.D.
Dwight O'Hara, M.D. Robert W. Buck, M.D.
Fletcher H. Colby, M.D. Herrman L. Blumgart, M.D.
Robert L. Goodale, M.D. Frank N. Allan, M.D.
Chester M. Jones, M.D. Harvey A. Kelly, M.D.
Harvey R. Morrison, M.D. Langdon Parsons, M.D.
Maxwell Firland, M.D. Mark Aisner, M.D.
Vernon P. Williams, M.D. Dale G. Friend, M.D.
Benjamin Castleman, M.D. Richard Warren, M.D.

MANUSCRIPTS, including references or bibliography, should be typewritten double spaced and submitted as original copy. References should conform to the style of the *Quarterly Cumulative Index Medicus* (listing name and initials of author, title of article, journal, volume number, first and last pages and year), and should be cited numerically in the order in which they appear in the text; the number should be limited to the absolute minimum.

ILLUSTRATIONS are reproduced as half tones and zinc etchings. Photographs must be distinct, and drawings done in black ink on white paper and each properly labeled.

MATERIAL printed in the *New England Journal of Medicine* is covered by copyright. Articles are accepted for consideration with the understanding that they are contributed for publication solely in this journal. The *Journal* does not hold itself responsible for statements made by any contributor.

MATERIAL, other than original articles, should be received not later than noon on Thursday, three weeks before date of publication.

COPY for advertisements is accepted by the advertising committee of the *Journal* on the basis of the apparent quality and usefulness of the product and the manner of its presentation. Proprietary names of pharmaceutical products must be accompanied by the chemical, or generic or official names, and the quantity of all active substances and the recommended dose must be stated. Copy should be factual, conservative and in good taste.

ALTHOUGH it is believed that all advertising material accepted conforms to ethical medical standards, acceptance does not imply endorsement by the *Journal*.

SUBSCRIPTION TERMS: $8.00 per year in advance, postage paid, for the United States (residents, interns and medical students, $5.00 per year); Canada, $9.00 per year (Boston funds); foreign, $10.50 per year. Long-term rates: United States, 2 years $15.00, 3 years $22.00; Canada, 2 years $17.00, 3 years $25.00; foreign, 2 years $20.00, 3 years $29.50.

MICROFILM volumes available to regular subscribers through University Microfilms, 313 N. First Street, Ann Arbor, Michigan.

COMMUNICATIONS should be addressed to the *New England Journal of Medicine*, 8 Fenway, Boston 15, Massachusetts. Telephone KE 6-2094.

INTERNATIONAL CONGRESS ON HEMATOLOGY

IT is altogether fitting that Boston, long known not only as the home of the bean and the cod but as the abiding place of Cabot, Wright, Minot and Murphy, of Castle and Cohn and travel-stained Dameshek, should be the city in which the International Society of Hematology should go on location next month. The occasion, of supreme scientific importance, will be the Sixth Biennial Congress of the Society, which will be held under the presidency of Dr. William Dameshek, at the Hotel Somerset during the week of August 26.

This will be the first international congress to be held in Boston since the International Physiological Society met in this city in 1929; many foreign physicians from many lands are expected to attend, as well as a full quota from beyond the Iron Curtain. This will include 7 Russian hematologists as well as others from Czechoslovakia, Poland and Hungary. Perhaps it is not too much to hope that through such an agency as the Congress the well known curtain may be reduced to some ferrated compound of more general hematinic value than at present.

The Congress of the International Society of Hematology will be immediately succeeded by the Sixth Congress of the International Blood Transfusion Society, under the presidency of Dr. I. S. Ravdin. This society will meet from September 3 to September 5, in conjunction with the American Association of Blood Banks. The two congresses will meet jointly on Saturday, September 1, and Monday, September 3, to discuss the first day the "auto" type of immunohematology and on the second the "iso" phase of the same subject.

Four languages will be used — English, French and Spanish as spoken tongues and Interlingua, in which *Blood*, under the editorship of Dr. Dameshek, has been interested — for documents, including programs and abstracts. The International Business Machines Corporation will supply the equipment to make simultaneous translations with the minimum of participation by the congressional corps of expert translators.

The principal topics to be discussed at the Congress are: leukemia, nucleonics, the spleen and hypersplenism, hemorrhagic disorders, anemia and immunohematology. It is hoped that those in attendance at the various conclaves will not, before the meetings are over, react to a spot of blood after the manner of Lady Macbeth.

NEW TYPE OF SUMMER SCHOOL

THE shortage of practically all categories of scientists is by now familiar news to biologic as well as natural scientists; and the contemporary situation

has been pointed up recently in a symposium published in the *Scientific Monthly.** Because of this shortage, Harvard University's experiment in the summer of 1956 with a new type of summer course seeking to improve high-school science teaching will be watched with interest, especially by physicians, for the course has the guidance of the Harvard Medical School as well as the Graduate School of Education. The eight weeks' program in July and August is designed "to stimulate and renew the interest of high school science teachers" according to the deans of the two graduate schools, Dr. George P. Berry and Francis Keppel.

An attractive feature of the plan is that the course is offered at no expense to the teachers coming to Boston, sponsored as it is by the Atomic Energy Commission and the National Science Foundation. Nominated by their high schools, 19 candidates (three times that number applied) have been selected for participation in the course by a committee composed of members of Harvard's faculties of Medicine and Education. Seminars will be led by outstanding scholars, the pattern of instruction to be followed being similar to that recently adopted for the instruction of first-year graduate students in the basic medical sciences — anatomy, bacteriology, biochemistry, pathology, pharmacology and physiology; and emphasis will be given to the devising of laboratory experiments and demonstrations that can be used in the classrooms.

This is an experiment in the right direction, no doubt, although it does not hit directly at what Dr. Charles Dollard, of the National Science Board, calls the "central fact," that the annual demand for men trained in science and in engineering "exceeds the annual output of our colleges and universities by a considerable margin. And the steady decline in enrollment in our high schools and colleges gives rise to the fear that the situation is getting worse rather than better." Dr. Dollard speculates about the difference in the youthful mind between the popular image of the scientist a generation ago and today. The old image was a person composed of equal parts, so to speak, of Tom Swift, Thomas Edison and Ben Franklin. Today the concept of a scientist is "a man under pressure to get an assigned job done, hardly less subject to authority than an Army recruit."

Dr. Arthur S. Flemming, of the Office of Defense Mobilization, also turns to the schools rather than the colleges and emphasizes the fact that teachers' salaries have been so disgracefully low that they are closer to being penalties than incentives. Likewise, Dr. Allan Waterman, director of the National Science Foundation, looks to the general public for the recruits for science and makes a plea for an early education in the hard subjects "such as languages, and logic, and mathematics, and physics, and chemistry."

*Dollard, C., Flemming, A., and Waterman, A. T. Crisis in science education. *Scientific Monthly* **82**:277-293, 1956.

Perhaps the experiment at Harvard will eventually make itself felt where it is most needed — in the ranks of the aspirants rather than their teachers. In all events, it holds a particular interest for physicians, for it is taking place in a medical-school setting. The participants, in addition to stimulating the interest of their own students in science, will expectedly exert a favorable influence on the recruitment of promising new blood into the ranks of scientific workers in general and into those of physicians, in particular.

FIGURATIVELY SPEAKING

With the ingenuousness that sometimes attacks even mature persons, the editorial staff of the *Journal* is moved at long intervals to reveal to its public some of the facts of life as they pertain to the biologic statistics of medical-periodical publication.

These are the days when currency seems to agglutinate in an almost erythrocytic pattern, like Cadillacs behind a roadblock; the circulation of the *Journal,* responding to the same inflationary influences, has in its own way experienced a gentle upward trend. Thus, during June, the month of roses and of brides, it was delivered, in addition to some 6800 members of the Massachusetts Medical Society, to nearly 27,000 regular and over 8000 student subscribers.

The list of journals, both domestic and foreign, in many languages, with which exchanges are in effect is 141; the Boston Medical Library is the final repository of these periodicals as it is of the books, to the number of nearly 1000 a year, that come to the *Journal* for review. It is scarcely practical at the present time actually to review all of this number, but all are listed and the lists published as soon as possible after the text is received.

For the information of those subscribers who suffer from late delivery of their journals the business management, in its anguish, can only call attention to an achievement of the past two years. During that period, perhaps for the first time in modern history, each week's journals, almost without exception, have been printed, bound, addressed and delivered to the post office before a low setting sun marks the departure of the date of issue. Before that hour the entire edition has been consigned to the carrier that bears all second-class matter to its destination.

"UND RUHIG FLIESST DER RHEIN"

The Deutscher Bundesärztekammer — the German Medical Association — has risen from the ashes of a former period of glory and erected its new Bundesärztehaus in the ancient city of Cologne. The dedication of the new building took place on April 29, during the meeting of the Council Session of the World

Medical Association (Weltärzteverband), which was held in its meeting rooms.

In addition to serving as headquarters for the Bundesärztekammer the new building will house the offices of the *Ärztliche Mitteilungen*, its journal, which appears on the interesting schedule of thirty-six times yearly. Land has also been purchased adjacent to the new headquarters building, on which will be erected an administration building for the Kassenärztliche Bundesvereinigung.

Mr. Gibbon states in the Lancet, that the application of belladonna to the mamma is an excellent means of checking the secretion of milk. With a lotion consisting of half a drachm of the extract of belladonna to half a pint of water, he has succeeded in arresting the secretion in these protracted cases, where a variety of expedients had failed.

Boston M. & S. J. *July 31, 1856*

MASSACHUSETTS MEDICAL SOCIETY

COMMITTEE ON MATERNAL WELFARE

Intestinal Obstruction after Cesarean Section

A thirty-three-year-old gravida II, para I, had had a cesarean section for premature separation of the placenta two years before. The postoperative course had been complicated by wound dehiscence on the fourth day, but she recovered. Recently, she had been hospitalized for intestinal obstruction, but not operated on. On the fifth day of her last menstrual period she was again hospitalized, and laparotomy was performed. The small bowel was accidentally opened when the abdomen was entered since it was adherent to the abdominal wall, but there was no true intestinal obstruction. Conception occurred two weeks later.

The pregnancy was uncomplicated. At thirty-eight weeks a repeat section was performed under spinal anesthesia, a normal infant being delivered. Great delicacy was used in the handling of all viscera.

With only occasional vomiting, abdominal pain and distention, which were appropriately treated with good effect, the pulse and temperature became normal. For six days the surgeon considered the postoperative course satisfactory.

On the seventh postoperative day, distention and gas pains increased, and the patient complained of pain in the back radiating to the shoulder. Poultices, an enema and a Levin tube were ineffective, but the pulse and temperature remained normal for two days.

On the ninth day, she quite suddenly became much worse. Shoulder and abdominal pain was excruciating; repeated narcotics afforded little relief. Distention became much worse and did not respond to treatment. The pulse was 140, and the temperature 101°F. The systolic blood pressure fell to 80-90. A Miller–Abbott tube, intravenous administration of fluids, penicillin and streptomycin were used. A surgical consultant described the patient as acutely ill, almost moribund, and lying very quietly on her back with a pinched expression and mottled color. She was alert and apprehensive, with a pulse of 180. Tympany extended all the way to the nipple line. There was no peristalsis. The wound was dry. Blood was started in a cut-down, and the abdomen opened under local anesthesia. Volumes of foul gas escaped as the abdomen was opened, and a large amount of intestinal contents was aspirated from the peritoneal cavity. Exploration revealed diffuse peritonitis and a large subdiaphragmatic abscess on the right, no old adhesions and, in the ascending colon, just above the cecum, a 5-mm. defect through which fecal contents were escaping. The surgeon was unable to exteriorize the involved segment because it was so friable. The hole was therefore closed around a catheter brought out via stab wound.

Postoperatively, the patient's condition worsened, and she died about twelve hours later.

This case defies the usual classification in preventability. Three members of the Committee called it nonpreventable, and 1 preventable, and 3 others were undetermined. This fact is scant consolation to the obstetrician and surgeons who struggled to keep the patient alive, but it is offered to illustrate the fact that no committee is in a position to be dogmatic about the difficulties of others.

Reduced to the simplest terms, it might be said that the patient died because she had had a previous cesarean section. To be sure, the initial cesarean was imperative and was probably done under duress and possibly in great haste since premature separation of the placenta is a critical emergency. Apparently, wound sepsis was followed by dehiscence. In retrospect the next laparotomy was unnecessary, although well advised. It certainly added to her later risks. One wonders whether pelvic delivery was possibly contemplated despite the initial cesarean section, with the purpose of avoiding further insult to the peritoneal cavity. This is not to imply that this *should* have been done since pelvic measurements are not available, and there could have been considerable apprehension about the uterine scar in a patient with a wound that was septic after a previous section.

From the time of the second section the patient's doom was apparently sealed when postoperative ob-

struction developed. Since her condition suddenly worsened on the seventh day, she might well have been reoperated on immediately instead of two days later, when almost moribund. Aside from a natural reluctance to perform yet another operation on so sick a patient, there is nothing in the record to justify the delay. With the value of all this hindsight, one might say that, technically, the death was "preventable," but majority opinion did not sustain this highly academic position, and there seems very little further constructive criticism to be offered.

JOHN FIGGIS JEWETT, M.D.
Chairman

NOTICES

SOCIETY MEETINGS AND CONFERENCES

JULY 31–AUGUST 28. Consultation Clinics for Crippled Children in Massachusetts. Page 1244, issue of June 28.

AUGUST 19–23. American College of Chest Physicians. Page 840, issue of November 10.

SEPTEMBER 3–5. Congress on Blood Transfusion, Blood Banks and Hematology. Page 297, issue of February 9.

SEPTEMBER 3–7. First Inter-American Conference on Occupational Medicine and Toxicology. Page 152, issue of July 19.

OCTOBER 8–13. International Cancer Cytology Congress. Page 104, issue of July 12.

OCTOBER 19 and DECEMBER 14, 1956, and FEBRUARY and APRIL, 1957. Massachusetts Society for Research in Psychiatry. Page 56, issue of July 5.

OCTOBER 30 and 31 and NOVEMBER 1. New England Postgraduate Assembly, Boston.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, AUGUST 2

THURSDAY, AUGUST 2

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Dr. John Spellman and staff. Saint Elizabeth's Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Medical Grand Rounds. Dr. Sylvester McGinn and staff. Saint Elizabeth's Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:00 m. Clinicopathological Conference. Dr. Benjamin Castleman and associates. Pathology Amphitheater, Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Surgical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*12:15–1:15 p.m. Orthopedic Clinic. Amphitheater, Peter Bent Brigham Hospital.
*3:00 p.m. Thoracic Conference. Cardiac Resuscitation: Policies for General Hospitals. Dr. Dwight E. Harken. Main Amphitheater, Peter Bent Brigham Hospital.

FRIDAY, AUGUST 3

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m. Pediatric Grand Rounds. Thorndike Amphitheater, Boston City Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*2:00–3:00 p.m. Pathology Conference. Dr. James Graham. Saint Elizabeth's Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.
*4:30 p.m. Neuroradiologic Conference. X-Ray Conference Room, New England Deaconess Hospital.

SATURDAY, AUGUST 4

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:30–10:00 a.m. Orthopedic Staff Conference. Boston City Hospital.
*8:30–10:00 a.m. Surgical Grand Rounds. Drs. Charles G. Child, III, A. J. A. Campbell and staff. First (Tufts) Surgical Service, New Cheever Amphitheater, Dowling Building, Boston City Hospital.
*9:30–11:00 a.m. Surgical House Officers' Conference. Second-Floor Conference Room, Carney Hospital, Dorchester.
*10:30 a.m. Teaching Ward Rounds. Ward South 2, Free Hospital for Women.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.

MONDAY, AUGUST 6

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:30–9:30 a.m. Clinic by Entire Surgical Staff and Anesthesia Staff, New Cheever Amphitheater, Dowling Building, Boston City Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:30 p.m. Staff Conference. Child Psychiatry. By appointment. Conference Room (Burnham 7), Massachusetts General Hospital.
*12:15–1:15 p.m. Clinicopathological Conference. Main Amphitheater, Peter Bent Brigham Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. X-Ray Conference. Dr. William Carey. Saint Elizabeth's Hospital.
*3:00–4:00 p.m. Neuroradiologic Conference. Dr. Bertram Selverstone. Stearns Auditorium, New England Center Hospital.
*4:00 p.m. Clinicopathological Conference. Pathology Conference Room, Beth Israel Hospital.
*4:00–5:30 p.m. Anesthesiology Conference. Surgical Conference Room, Peter Bent Brigham Hospital.
*5:00–6:30 p.m. Anesthesia Group of the Lahey Clinic. Joslin Auditorium, New England Deaconess Hospital.

TUESDAY, AUGUST 7

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical Grand Rounds. Pathology Conference Room, Carney Hospital, Dorchester.
*10:30 a.m. Medical Grand Rounds. Main Conference Room (Ground Floor), Lemuel Shattuck Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m.–1:00 p.m. Pediatric Grand Rounds. Burnham Memorial Hospital for Children (Burnham 4), Massachusetts General Hospital.
*12:15–1:15 p.m. X-Ray Conference. Dr. Merrill Sosman. Main Amphitheater, Peter Bent Brigham Hospital.
12:30–1:30 p.m. Medical Journal Club. Joslin Clinic. (Cafeteria) New England Deaconess Hospital.
*2:00–3:00 p.m. Hematology Conference. Dr. Mario Stefanini. Saint Elizabeth's Hospital.
*4:00–5:30 p.m. Anesthesia Conference. Dr. Benjamin Etsten. Stearns Auditorium, New England Center Hospital.
*5:00 p.m. Surgical Journal Review. Mount Auburn Hospital, Cambridge.
*5:00–6:00 p.m. Service Meeting Followed by Clinical Conference (Medical, Surgical, Obstetric). Faulkner Hospital.

WEDNESDAY, AUGUST 8

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Medical and Surgical Clinic on Diabetic Problems. Deaconess II, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Auditorium, Carney Hospital, Dorchester.
*9:00–10:00 a.m. Surgical Grand Rounds. Massachusetts Memorial Hospitals.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m. Orthopedic Grand Rounds. Bigelow Amphitheater, White 3A, Massachusetts General Hospital.
*12:00 m.–1:00 p.m. Boston State Hospital Psychiatry Seminar. Reception Building Auditorium, 591 Morton Street, Dorchester.
*12:00 m.–1:00 p.m. Roentgen Diagnostic Conference. 5th-floor teaching unit, Beth Israel Hospital.
*12:00 m.–1:00 p.m. Pediatric Clinicopathologic Conference. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*12:15 p.m. Vascular Rounds. Drs. Edward A. Edwards and Chilton Crane. D-Main, Peter Bent Brigham Hospital.
*12:30 p.m. Weekly Pathological Meeting. Joslin Auditorium, New England Deaconess Hospital.
*12:30–1:30 p.m. Weekly Staff Review of Autopsies. Dr. William A. Meissner. Joslin Auditorium, New England Deaconess Hospital.
*1:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*1:00 p.m. Massachusetts General Hospital Hand Clinic. The Clinics of the Massachusetts General Hospital.
*2:00 p.m. Rectal Clinic. Peter Bent Brigham Hospital.
*2:00–3:00 p.m. Pediatric Conference for Practitioners. Jimmy Fund Building, Children's Medical Center, 35 Binney Street.
*4:00–5:30 p.m. Fracture Lecture. Boston City Hospital.
*4:00–6:00 p.m. Overholt Thoracic Conference. Joslin Auditorium, New England Deaconess Hospital.
*6:00 p.m. Alcoholism Clinic. Peter Bent Brigham Hospital.
*7:30–9:30 p.m. Lahey Clinic Lecture. Joslin Auditorium, New England Deaconess Hospital.

*Open to the medical profession.